Novel amino acid synthons based on ketene thioacetals

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Novel Amino Acid Synthons based on Ketene Thioacetals

submitted by William Osburn Moss

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ABSTRACT

This thesis is introduced by a review of the synthesis of ring-substituted prolines, which describes a variety of general and specific approaches to the problem of introducing substituents into the pyrrolidine ring in a stereocontrolled fashion. Our own approach to this area began with a study of some intermolecular 1,3-dipolarcycloaddition reactions of ketene thioacetals with electron-deficient azides, which gave three classes of product depending on the substituents present, and the results of this study are described in chapter 1. Chapter 2 is concerned with the development of an intramolecular azide-ketene thioacetal cycloaddition reaction which was used to prepare *racemic* proline. The cycloaddition reaction resulted in the formation of an unstable cyclic imine and various mechanistic studies helped to shed light on the structure of this compound.

The scope and limitations of the intramolecular cycloaddition reaction are described in chapter 3, including the results of varying the substituents present in the cyclisation precursor and varying the conditions used to trap the cyclisation product. The cycloaddition reaction was also used to prepare pipecolic acid, the six-membered ring homologue of proline.

Chapter 4 describes the application of the intramolecular cycloaddition reaction to the synthesis of (2S, 3S, 4R)-3,4-dihydroxyproline. The ring substituents were introduced before the cyclisation step and the cyclic imine, formed by the cyclisation reaction, was reduced stereoselectively, thus providing control of the stereochemistry at C-2 of the product. Chapter 5 describes a complimentary approach to the synthesis of substituted prolines in which the substituents were introduced after the cyclisation reaction. A cyclic α-aminoketene thioacetal prepared by cycloaddition, itself a derivative of proline, was deprotonated to give a sulphur-stabilised allylic anion. This

anion reacted with a range of electrophiles at the γ-site, corresponding to C-3 of proline. Hydrolysis of the ketene thioacetal group then gave a range of *racemic*-3-substituted prolines which had substantially or exclusively *trans*-relative stereochemistry. The overall process represents the formation and alkylation of the homoenolate of proline.

The final chapter describes some miscellaneous results encountered during this study, including various reactions which involved sulphur-participation or -migration.

Acknowledgements

I would like to thank my supervisors, Drs. Tim Gallagher, Rob Bradbury and Neil Hales, for their constant support and enthusiasm throughout the three years spent on this thesis. Without them, none of the work described below would have been possible. Likewise, I am indebted to S.E.R.C. and I.C.I. Pharmaceuticals for generous financial support, and to Bath University for providing research facilities. In addition, I would like to thank all members of the chemistry departments at Bath University and at Alderley Park who have shown friendship and provided advice over the years. In particular, I am grateful to Tim Donohoe and Emma Wakefield for the contributions which they made to this project during their respective final years as undergraduates at Bath. I would like to thank Dave Wood, Harry Hartnell, Alan Carver and Chris Cryer for running NMR and mass spectra and for performing elemental analyses, also Sue Boucher, John Bradley and Russel Barlow for providing technical assistance. Finally, I am extremely grateful to Mrs. Jo Curtis for typing this thesis.

Abbreviations

Ac	Acetyl
BDP	Bis(dimethylaluminium)propane-1,3-dithiolate
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
b.p.	Boiling point
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl (*tert*-butyl)
Bz	Benzoyl
cat.	Catalyst
CBZ	Carbobenzyloxy
CDI	Carbonyl diimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulphoxide
Et	Ethyl
HOMO	Highest occupied molecular orbital
hr.	Hour
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LTMP	Lithium tetramethylpiperidide
Me	Methyl
m.p.	Melting point
NCS	N-Chlorosuccinimide

NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Ph	Phenyl
PhFl	9-Phenylfluorenyl
n-Pr	*n*-Propyl
Pv	Pivaloyl (2,2-dimethylpropanoyl)
Py.	Pyridine
Recryst.	Recrystallized
r.t.	Room temperature
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflic (trifluoromethanesulphonic)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
Ts	Tosyl (*p*-toluenesulphonyl)

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INTRODUCTION

Introduction-The Synthesis of Ring Substituted Prolines

Part 1. Introduction.

Part 2. 2-Substituted prolines.

Part 3. 3-Substituted prolines.

Part 4. 4-Substituted prolines.

Part 5. 5-Substituted prolines.

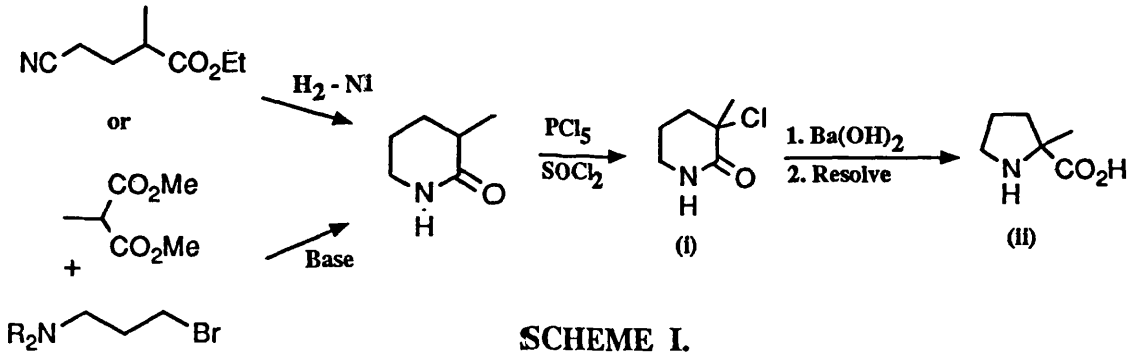
Part 6. Polysubstituted prolines.

- (i) 3,4-Dihydroxyproline.
- (ii) The kainic acids.
- (iii) Other disubstituted prolines.
- (iv) Tri- and polysubstituted prolines.

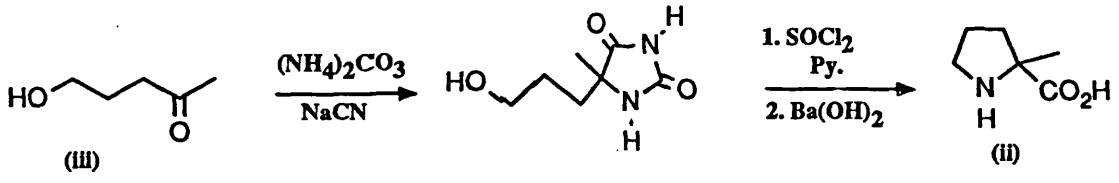
Part 7. Introduction to the results and discussion.

Part 1. Introduction

This review covers the synthesis of proline derivatives with substituents at C-2, C-3, C-4 and C-5. The area was reviewed by Mauger and Witkop in 1966[1], but no review concerned specifically with proline derivatives has been published since then. However, an intense effort has continued to be directed towards the synthesis of amino acids in general, and a monograph on the synthesis of optically active α-amino acids was recently published by Williams[2]. The review which follows is not exhaustive but aims to cover all of the important developments in the synthesis of substituted prolines. Some 2-(hydroxymethyl)pyrrolidines and other proline derivatives are also included but proline derivatives which differ only in their nitrogen- and carboxylic acid-substituents are excluded. A substantial amount of the work described in this thesis is concerned with the synthesis of proline and various proline derivatives, and it is intended that the introduction should give the reader an indication of the methodology which already exists in this area. It is noteworthy that techniques for funtionalizing the basic proline nucleus at C-2, C-4 and C-5 are known, but no general methods are known for functionalization of proline itself at C-3.



SCHEME I.



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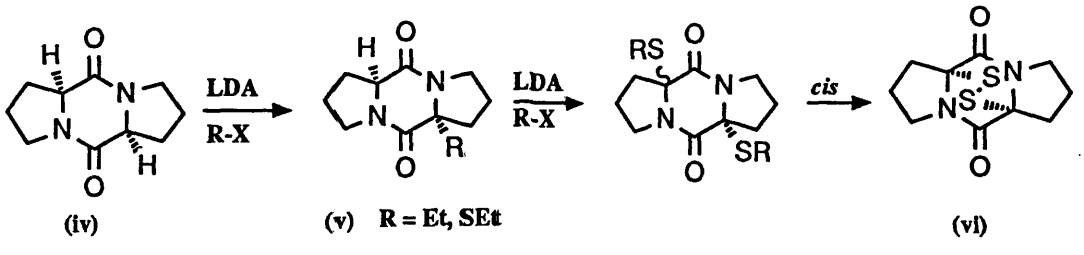


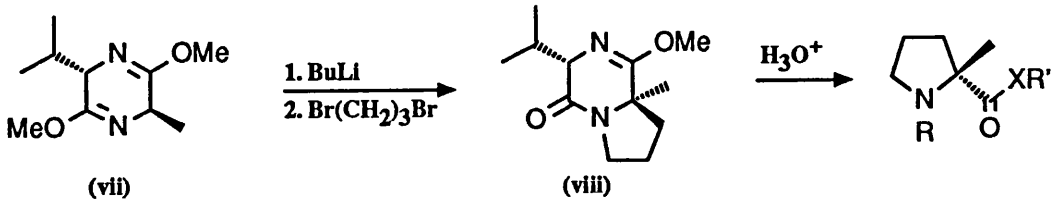
SCHEME III

Part 2. 2-Substituted Prolines

The first reported syntheses of 2-substituted prolines were not enantioselective and so relied on classical resolution to obtain optically active material. The base-induced rearrangement of 3-halopiperidin-2-ones has provided a general route to a number of substituted prolines, by introducing substituents into the piperidine ring prior to rearrangement. Racemic 2-methyl proline (**ii**) was first prepared by Kariyone in 1960, by rearrangement of 3-methyl-3-chloropiperidin-2-one (**i**) (Scheme I)[3]. This route was adapted by Overberger *et al* who used quinine to resolve the product, thus providing optically active 2-methylproline[4]. Another approach to racemic (**ii**) was to use the Strecker reaction starting from 5-hydroxypentan-2-one (**iii**). The Strecker reaction converted the carbonyl group of (**iii**) to the corresponding amino acid and this was followed by cyclization to give the pyrrolidine ring [5] (Scheme II).

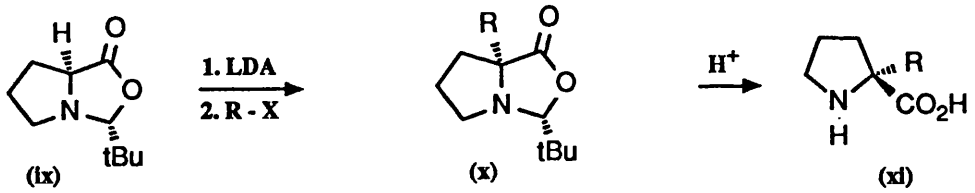
Alkylation of an enolate derived from proline provides a general route to 2-substituted prolines. The asymmetric variant of this process was first described by Schmidt and Poisel who used the diketopiperazine of proline (**iv**) to prepare various optically active 2-substituted proline derivative[6]. Selective monodeprotonation of (**iv**) followed by alkylation with carbon- or sulphur-electrophiles occurred with retention of configuration to give (**v**) (Scheme III). Sequential dialkylation of (**iv**) gave mostly the *trans* (*meso*) product but the *cis* dithiol was used to prepare the cyclic disulphide (**vi**), an analogue of aratonin.

The stereocontrolled alkylation of the enolate prepared from (**iv**) uses the second proline molecule as a chiral auxiliary. It is interesting to note that the chiral centre present in proline is lost during enolate formation, but the second proline molecule provides an "asymmetric memory". A similar approach has been used extensively by Schöllkopf to prepare amino acid derivatives, including 2-methyl proline (**ii**)[7]. Sequential C- and N- alkylation of (**vii**) gave the proline derivative (**viii**)

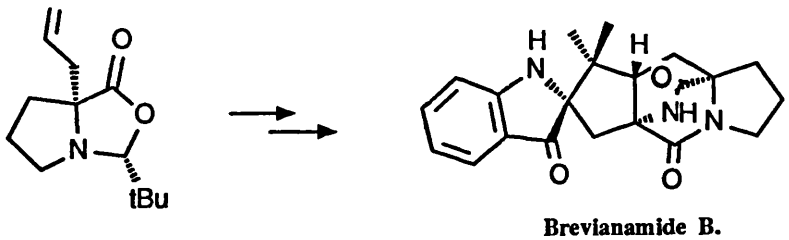


(vii) (viii)

SCHEME IV

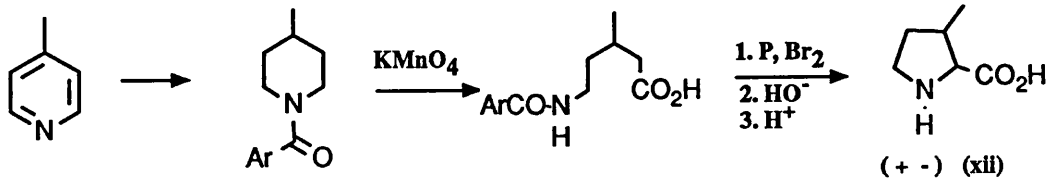


(ix) (x) (xi)



Brevianamide B.

SCHEME V

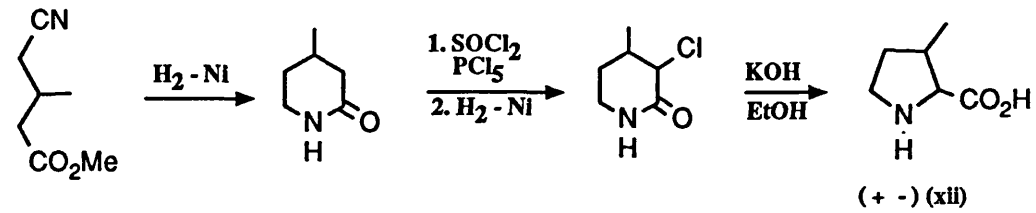


(+ -) (xii)

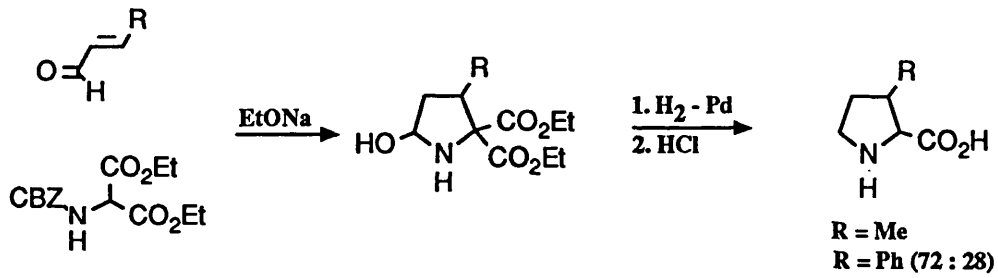
SCHEME VI

with high diastereoselectivity. Selective hydrolysis of either the amide or amidate group then led to either Pro-Val or Val-Pro as desired (Scheme IV).

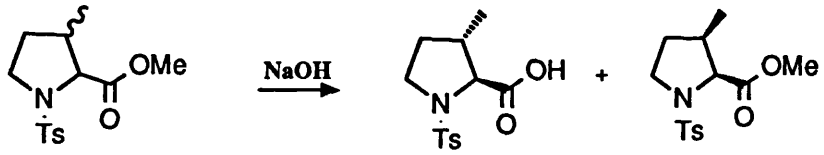
Seebach has made extensive use of the concept of stereocontrol based on temporary stereocentres (chirality transfer), and has applied this idea to the synthesis of 2-substituted prolines[8]. The cyclic aminal (**ix**) could be deprotonated to give the corresponding enolate which was alkylated with a wide range of electrophiles and in each case the alkylation occurred exclusively on the same face as the *tert*-butyl group. The adducts (**x**) were then hydrolysed to give 2-substituted prolines (**xi**) of high enantiomeric purity (Scheme V). 2-Allylproline prepared in this way was recently used as the starting material for the synthesis of the natural product brevianamide B[9], and the variety of electrophiles used by Seebach clearly demonstrates the generality of this route to 2-substituted prolines.



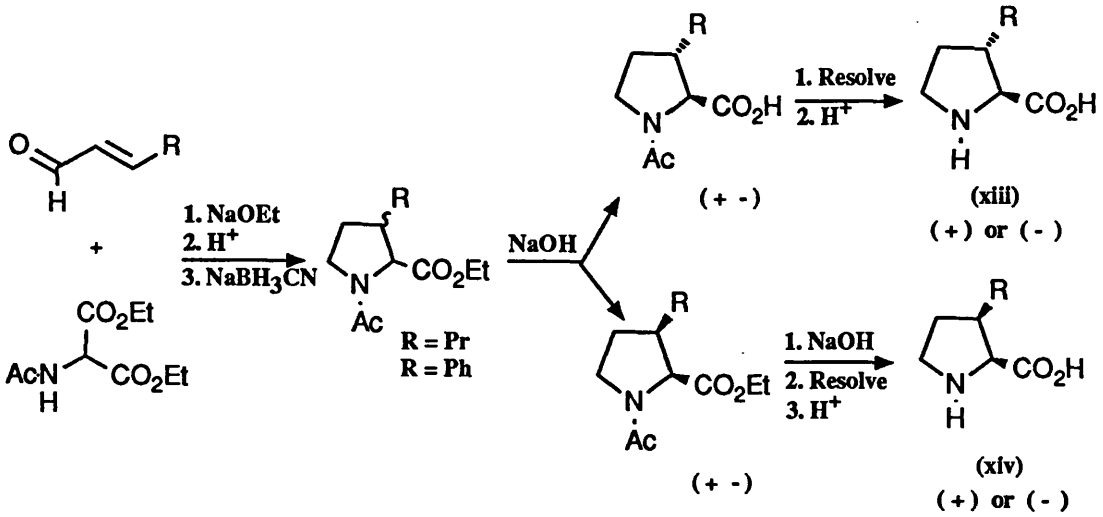
SCHEME VII



SCHEME VIII



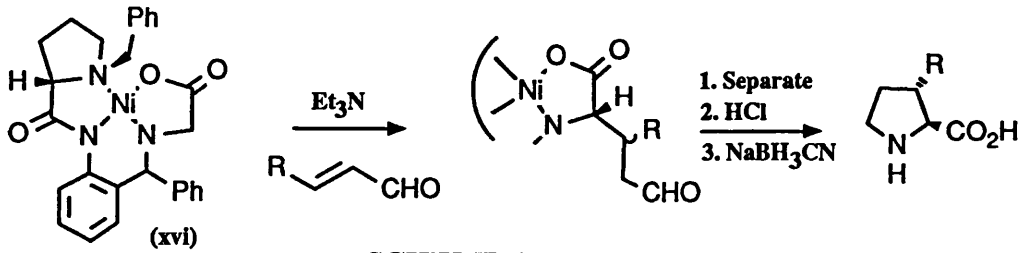
SCHEME IX



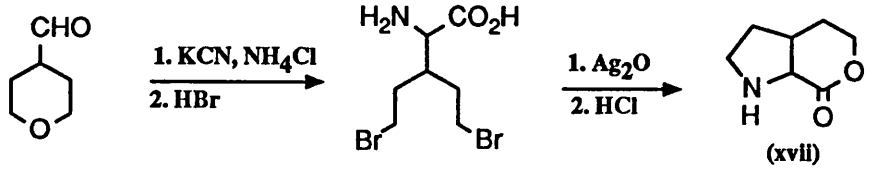
SCHEME X

Part 3. 3-Substituted Prolines

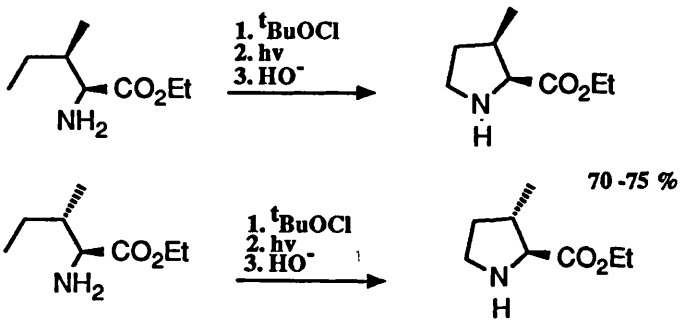
By analogy with the route to 2-substituted prolines described above, 3-substituted prolines can be prepared by halogenation then rearrangement of 4-substituted piperidin-2-ones. In 1944 Adams and Leonard reported a synthesis of *racemic* 3-methyl proline (**xii**) based on this strategy[10] (Scheme VI). In this case the carbon skeleton was prepared by catalytic hydrogenation of 4-methylpyridine. A similar approach to *racemic* (**xii**) was described by Kariyone[11] (Scheme VII). Condensation of N-acyl-2-aminomalonic acid derivatives with α,β-unsaturated aldehydes provides a general route to ring-substituted prolines. Sequential (1,4) and (1,2) addition of the aminomalonic acid derivative to the aldehyde leads to a 5-hydroxyproline which can be reduced to give the corresponding proline. Substituted α,β-unsaturated aldehydes then lead to substituted prolines, and use of β-substituted-α,β-unsaturated aldehydes provides a route to 3-substituted prolines. This method was first used by Cox *et al* to prepare 3-methyl- and 3-phenylproline as mixtures of diastereoisomers[12] (Scheme VIII). An efficient technique for separation of the diastereomers of 3-methylproline was reported later by Mauger *et al* who found that hydrolysis of a mixture of *cis* and *trans* esters led to selective saponification of the *trans* diastereomer. Presumably, in this kinetic separation, unfavourable steric interactions prevent formation of the tetrahedral intermediate required for hydrolysis of the *cis* isomer[13] (Scheme IX). These techniques were very recently applied to the synthesis of 3-propyl- and 3-phenylproline[14]. In each case, after separating the diastereomers by selective saponification, the racemic *trans* compounds were resolved to give pure enantiomers (**xiii**). Prolonged saponification of the *cis* ester followed by resolution gave the two *cis* enantiomers (**xiv**), thus providing an efficient route to large quantities of diastereomerically and enantiomerically pure 3-substituted prolines (Scheme X). The authors also reported the preparation of proline-3-carboxylic acid by oxidation of the corresponding phenyl derivative using ruthenium tetroxide.



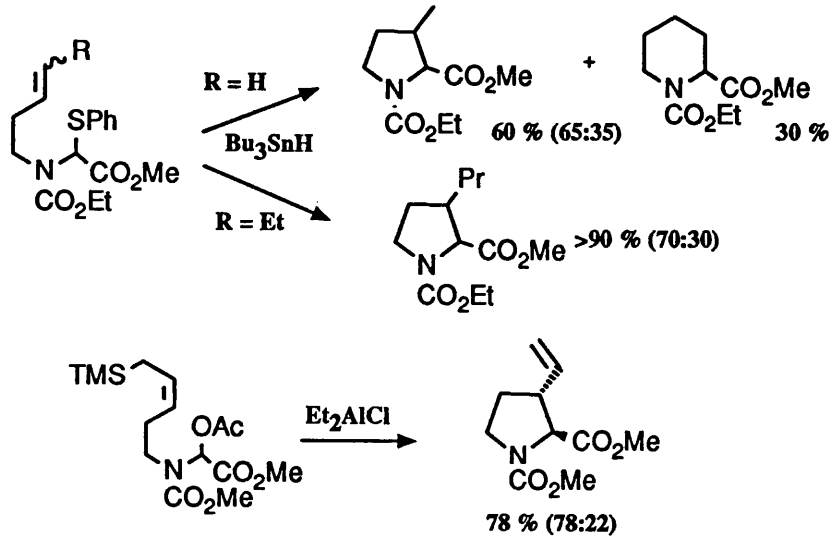
SCHEME XI



SCHEME XII



SCHEME XIII

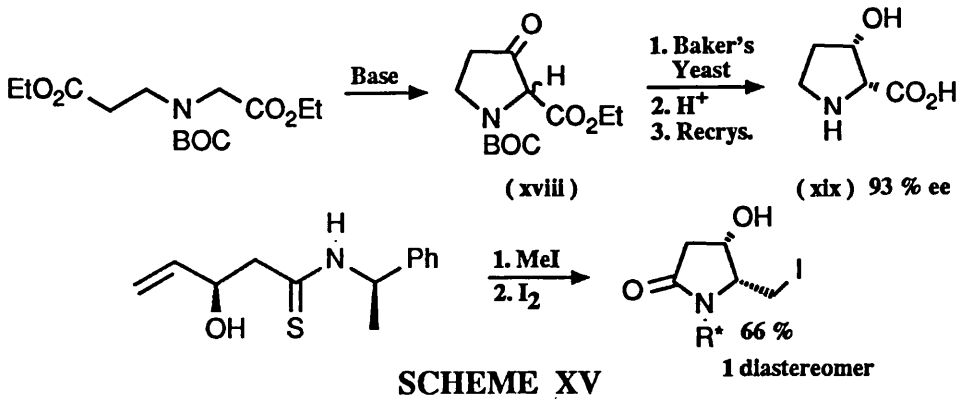


SCHEME XIV

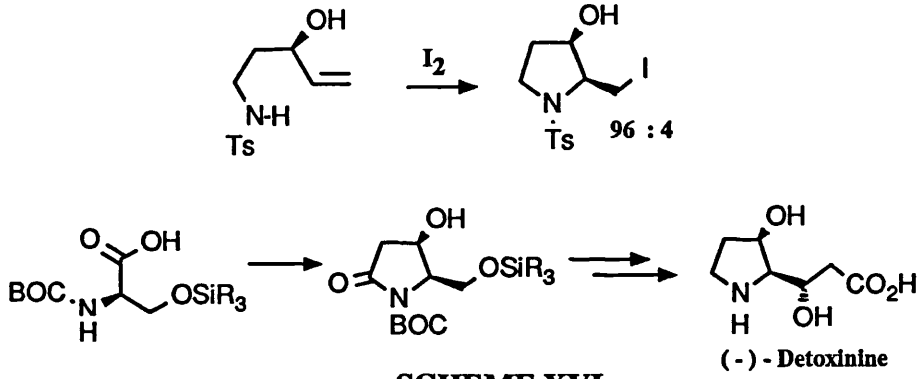
Belokon and co-workers have modified the method of Cox *et al* by replacing aminomalonic acid derivatives with the chiral nickel-glycine complex(**xvi**). This complex is essentially planar except for the N-benzylproline moiety which is thought to block one face of the glycine residue. Thus, alkylation of the enolate derived from (**xvi**) occurred predominantly on the unhindered face, and this route was used to prepare *cis*- and *trans*-3-methyl- and 3-phenylproline with optical purities of > 95%[14] (Scheme XI). The chiral centre at C_α of the products was controlled during the alkylation step, and separation of the C_β diastereomers by conventional means then led to optically pure *cis* or *trans* compounds as desired.

In addition to the two general routes to 3-substituted prolines discussed above, a variety of other approaches has also been described. Prelog reported a synthesis of *racemic* 3-(2-hydroxyethyl)proline lactone (**xvii**) based on the Strecker reaction[15] (Scheme XII). Titouani *et al* used isoleucine and alloisoleucine to prepare *cis*- and *trans*-3-methyl proline respectively. These transformations were based on N-chlorination of the amino acid derivative, followed by photolytic N-to-C transfer of chlorine via (1,5) radical abstraction, an example of the Hofmann-Loffler-Freytag reaction. In both cases this process occurred without epimerization so that ring closure led to optically pure products[16] (Scheme XIII). Recently Hiemstra, Speckamp and co-workers have described two different approaches to the synthesis of 3-substituted prolines which were designed to complement the normal reactivity of α-amino acids[17,18]. The two routes were based on the formation, and subsequent trapping, of either a radical or a carbocation at C_α, and were used to prepare 3-substituted proline derivatives with modest *trans* selectivity (Scheme XIV).

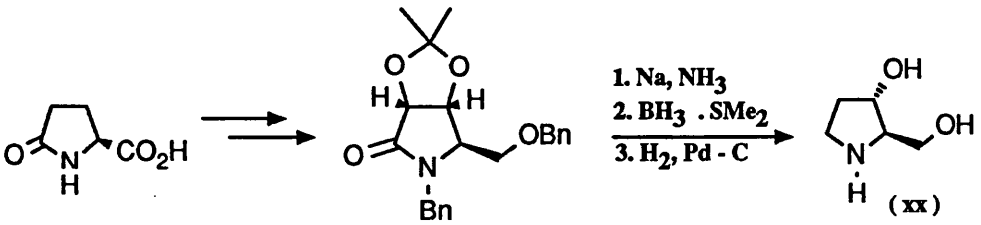
The presence of the 3-hydroxypyrrolidine group in a number of natural products has led to the publication of various approaches to 3-hydroxyproline over the last few years. For example, asymmetric reduction of *racemic* 3-oxoproline (**xviii**) using bakers' yeast gave substantially the diastereomer (**xix**) [19]. Evidently,



SCHEME XV



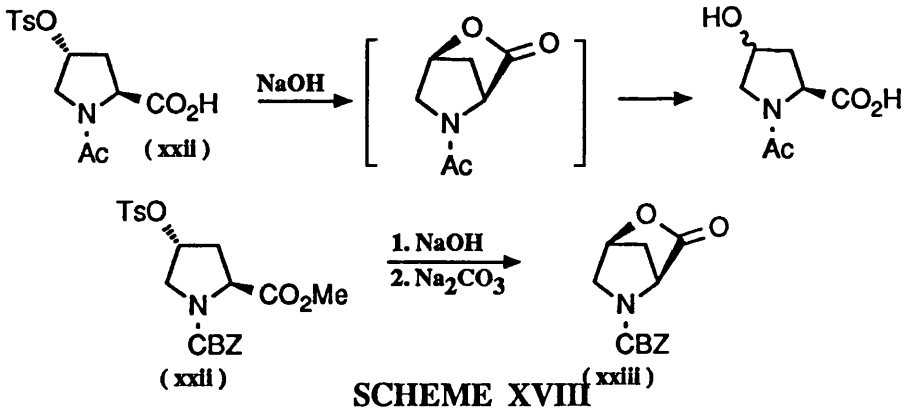
SCHEME XVI



SCHEME XVII

epimerisation of (**xviii**) was faster than reduction, resulting in a dynamic kinetic resolution of the *racemic* starting material. A closely related compound was prepared by iodolactamization of a substituted thioimidate which was reported to give only one diastereomer of product[20] (Scheme XV). A similar cyclisation to give the enantiomeric *cis*-compound also relied on a highly diastereoselective electrophile-mediated cyclisation[21]. A different approach was described by Joullie, who used serine to prepare (-)-detoxinine *via* a 3-hydroxyproline derivative [22]. In this case the stereochemistry at C_α was controlled by the choice of starting material, while the stereochemistry of the C_β-hydroxyl group was controlled by a stereoselective reduction (Scheme XVI). The *trans*-3-hydroxyproline derivative (**xx**) has been prepared in optically active form from D-glutamic acid. Stereoselective *cis*-dihydroxylation of 3,4-deydropyroglutamic was followed by selective reduction of both the C-4 hydroxyl group and the amide[23](Scheme XVII).

Finally, *racemic cis*-3-aminoproline has been prepared by hydrogenation of 3-nitropyrrole-2-carboxylic acid[24]. A general route to 3-substituted prolines, starting from proline, is described in chapter 5 of the results and discussion.



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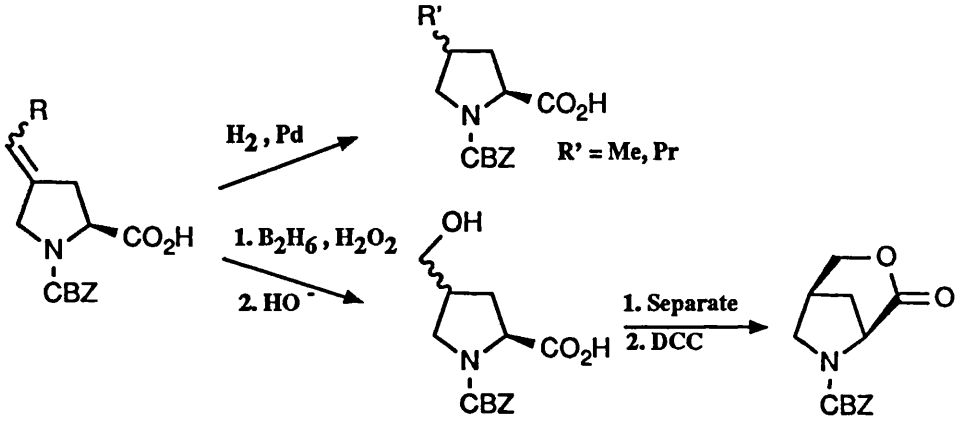
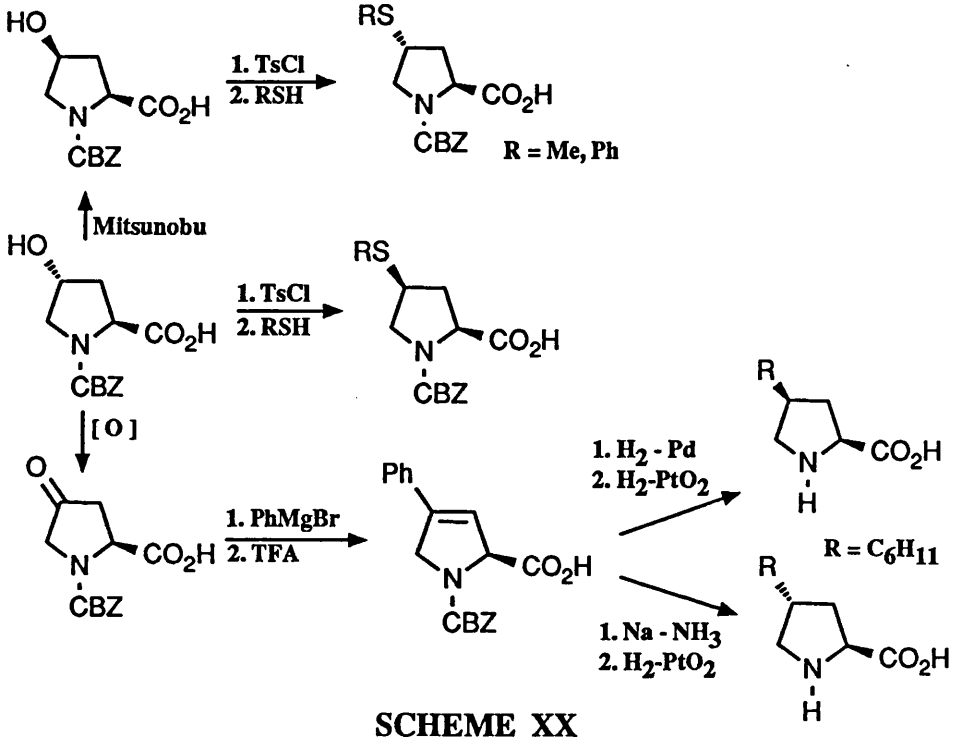


SCHEME XIX



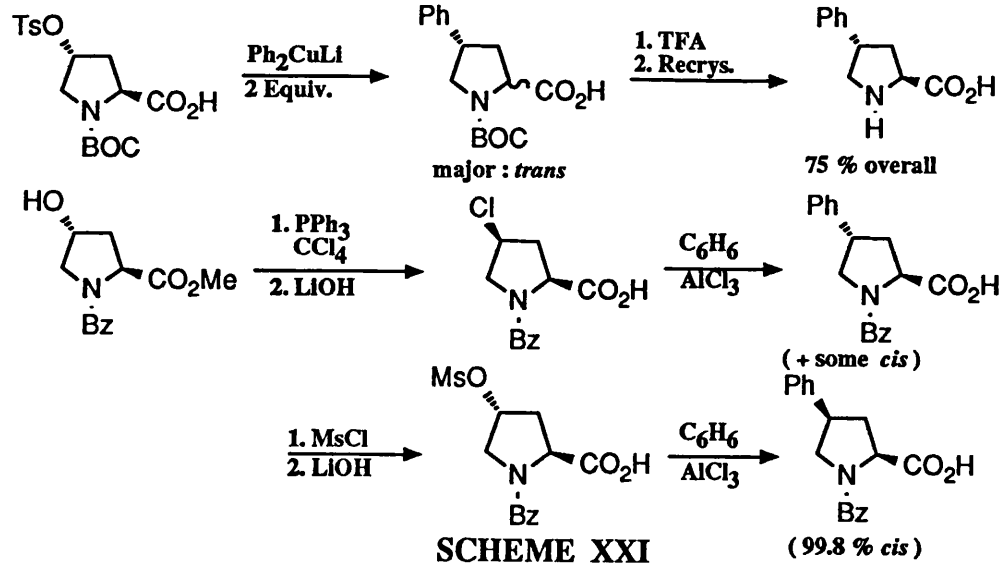
SCHEME XX

Part 4. 4-Substituted Prolines

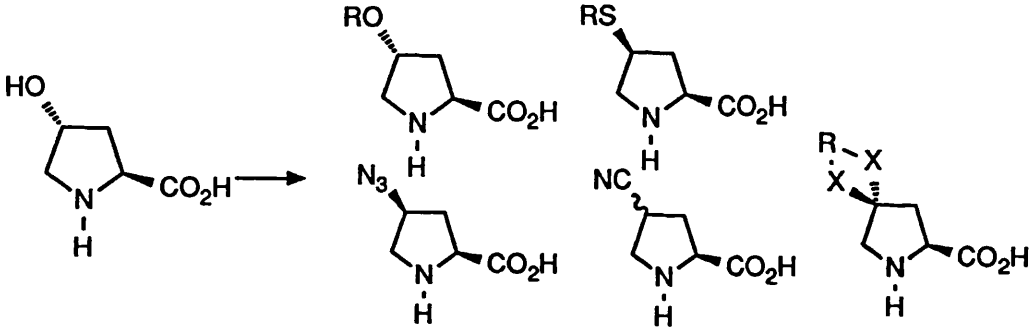
The earliest examples of the synthesis of 4-substituted prolines all started from the readily available 4-hydroxyproline (**xxi**). The relative stereochemistry of 4-hydroxyproline was originally established as *trans* by preparing the tosylate[24]. Hydrolysis of tosylate (**xxii**) was reported to give a mixture of epimers at C-4, suggesting participation of the carboxylic acid group in the hydrolysis process[25]. The postulated bicyclic intermediate could undergo either nucleophilic displacement at C-4 or lactone hydrolysis, and these two pathways lead to complementary stereochemistry at C-4. Controlled hydrolysis of the related tosylate (**xxiii**) allowed isolation of lactone (**xxiv**) (Scheme XVIII)[26]. 4-Hydroxyproline was also used to prepare *cis*-4-iodoproline by tosylate displacement[27], and *cis*-4-bromoproline by treatment of 4-hydroxyproline with phosphorus pentabromide[1].

Oxidation of 4-hydroxyproline led cleanly to the corresponding ketone (**xxv**)[25]. Reaction of this ketone with phosphonium ylides gave alkenes[28,29] which in turn underwent catalytic hydrogenation to give diastereomeric mixtures of 4-alkylprolines[29](Scheme XIX). The selectivity of these reactions was poor but, in each case, separation of the resulting diastereomers was possible. Hydroboration of 4-methyleneproline, followed by oxidation, led to 4-(hydroxymethyl)proline as a separable mixture of diastereomers[30]. The *cis* compound underwent cyclisation to give the corresponding lactone (Scheme XIX).

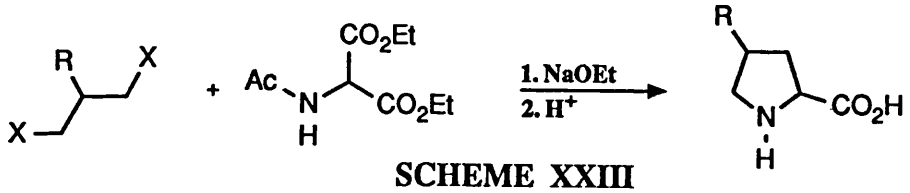
The recent discovery of the drug captopril[31] led to a renaissance of the chemistry of 4-hydroxyproline, spurred by the need to make a variety 4-substituted prolines which were subsequently used to modify the reactivity of captopril. Workers at Squibb prepared a number of compounds by tosylation or oxidation of 4-hydroxyproline, and also used the Mitsunobu reaction to invert the stereochemistry of 4-hydroxyproline at C-4, thus providing access to C-4 epimeric series[32](Scheme XX).



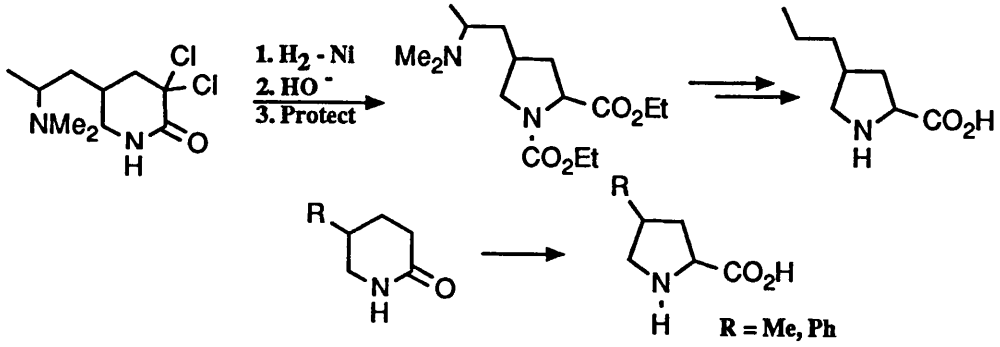
SCHEME XXI



SCHEME XXII



SCHEME XXIII

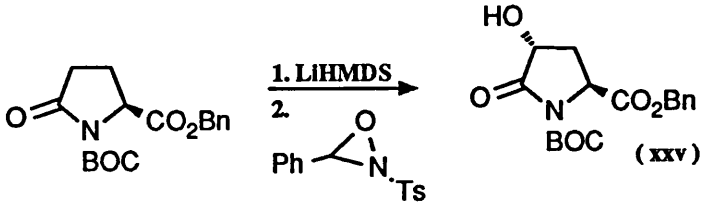


SCHEME XXIV

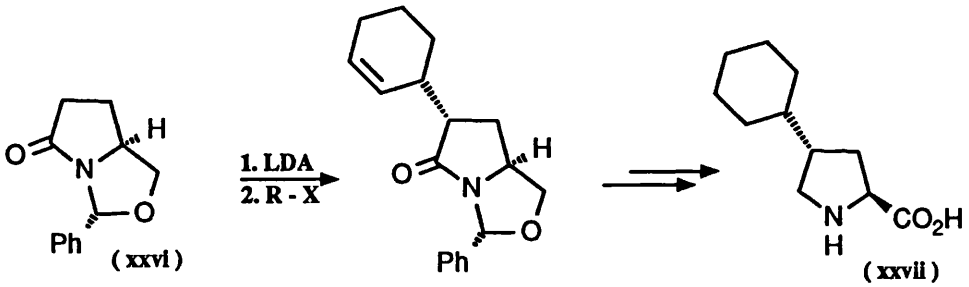
Different approaches to *cis*- and *trans*- 4-phenylproline were also published including the use of cuprates[33] and of the Friedel-Crafts reaction[34] (Scheme XXI). Cuprate displacement of the tosylate of 4-hydroxyproline proceeded with retention of configuration C-4 to give *trans* 4-phenylproline, indicating complete participation of the carboxylic acid group in the displacement reaction. On the other hand, Friedel Crafts-type substitution of the mesylate of 4-hydroxyproline proceeded with inversion of configuration at C-4, thus providing access to the complementary *cis* 4-phenylproline. Similar results have been published by workers from Merck who prepared a range of derivatives of proline starting from 4-hydroxyproline[35](Scheme XXII).

Early approaches to 4-alkylprolines which were not based on 4-hydroxyproline included the use of 2-aminomalonic acid derivatives[36,37,38]. The reaction of diethyl acetamidomalonate with α,β-unsaturated aldehydes (*vide supra*) has been applied to the synthesis of racemic 4-propylproline[29] and 4-methylproline[41], while Belokon *et al* have used their enantiomerically pure nickel complex to prepare optically active *cis*-and *trans*-4-methylproline. In addition to their reactions with α,β-unsaturated aldehydes, 2-aminomalonic acid derivatives also underwent sequential dialkylation when treated with 1,3-dihalopropanes, and use of symmetrical 2-substituted-1,3-dihalopropanes thus provided a route to 4-substituted prolines (Scheme XXIII). The rearrangement of 5-substituted-3-chloropiperidin-2-ones has been used to prepare 4-substituted prolines, and some examples of this reaction are shown in scheme XXIV[39,40,3]. Another route to optically active 4-methylproline made use of naturally occurring (4R)-5-acetoxy-4-methylpentanoic acid as starting material[41]. The chiral centre present in the starting material was transformed into C-4 of the product, thus controlling the absolute stereochemistry.

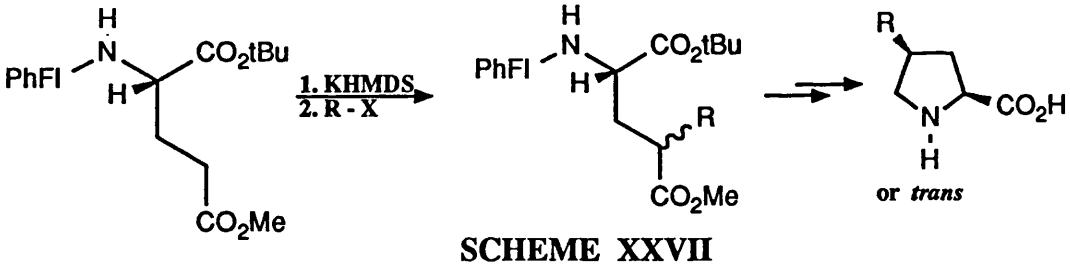
Pyroglutamic acid derivatives should provide a simple entry into 4-substituted prolines by regioselective enolate formation followed by stereoselective



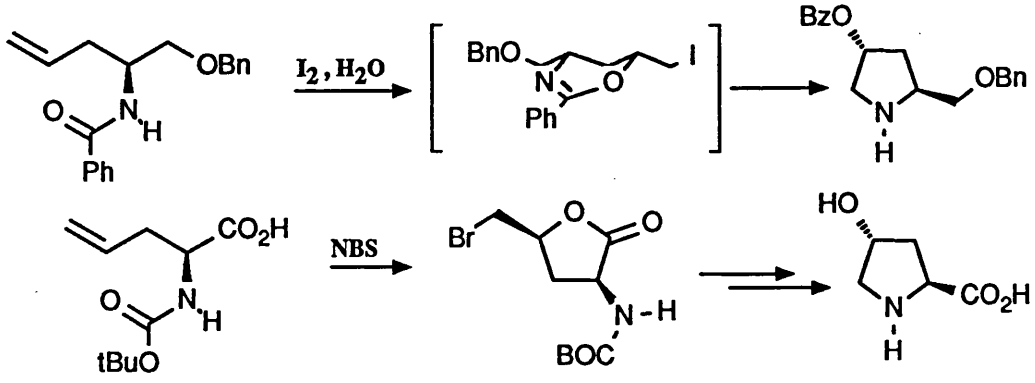
SCHEME XXV



SCHEME XXVI



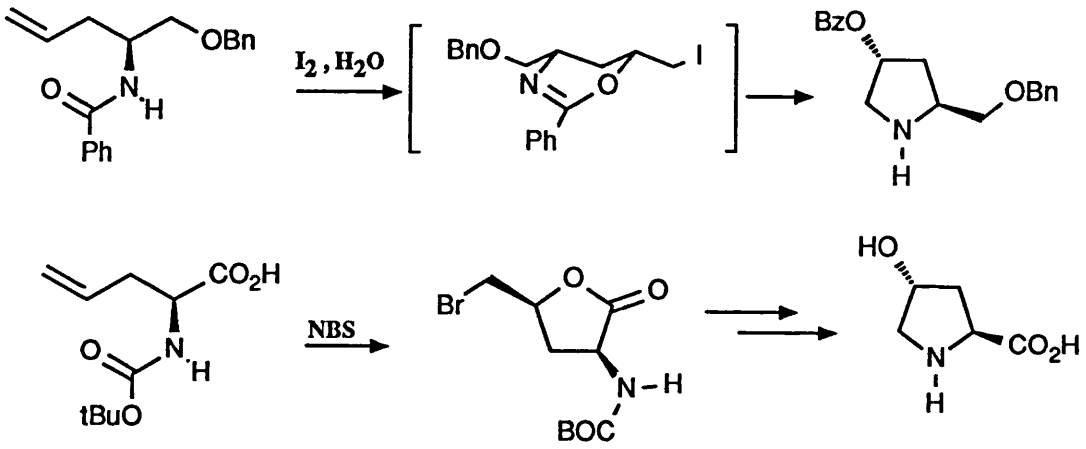
SCHEME XXVII



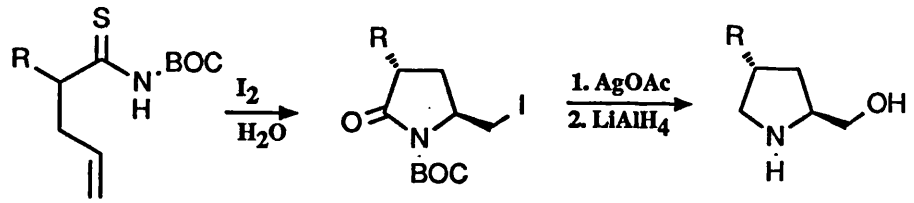
SCHEME XXVIII

alkylation. Reduction of pyroglutamic acid to give proline has been reported to occur in high yield and without racemization[42],thus substituted pyroglutamic derivatives should serve as precursors to substituted prolines. In spite of this, the sequential deprotonation/alkylation of pyroglutamic acid remains largely unexploited as a route to 4-substituted prolines, but was used for a synthesis of the 4-hydroxyproline derivative (**xxv**) using an oxaziridine as the electrophile[43] (Scheme XXV). In this case, oxidation of the enolate occurred exclusively *anti* to the ester group. Thottathil and co-workers pointed out the problems of regio and chemoselectivity as well as racemization associated with reactions of the type shown in Scheme XXV and they prepared the novel pyroglutamic acid derivative (**xxvi**) which was designed to overcome the problems mentioned above[44]. Deprotonation of (**xxvi**), followed by alkylation, gave only one diasteromer which was transformed into optically active *trans*-4-cyclohexylproline (**xxvii**) (Scheme XXVI). Reduction of the carboxylic acid group of pyroglutamic acid prior to enolate formation removed the problem of racemization and the rigid, bicyclic nature of (**xxvi**) ensured that alkylation occurred exclusively on the *exo*-face. A related approach, using glutamic acid rather than pyroglutamic acid, was described by Rapoport[45]. Regioselective alkylation of glutamic acid derivative (**xxviii**) gave a mixture of diastereomers, and was followed by reduction of the less hindered δ-ester then separation of the two diastereomers. The resulting aminoalcohol underwent cyclisation and deprotection to give either *cis*- or *trans*-4-substituted prolines (Scheme XXVII). This strategy relied on the use of different protecting groups to control the regiochemistry of deprotonation/alkylation, and required the separation of diastereomers to control the relative stereochemistry of the new chiral centre at C-4, thus it does not represent an ideal solution to the problem of preparing 4-substituted prolines. A related series of alkylations was carried out by Baldwin *et al*[46].

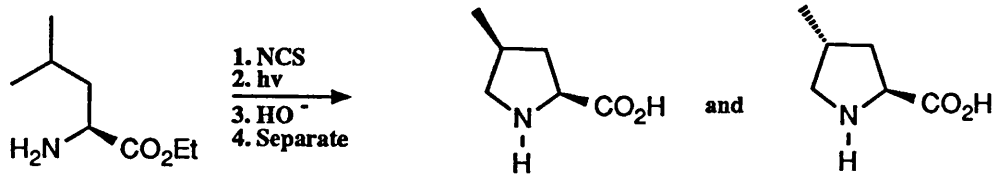
Electrophile-mediated alkene cyclisations have been used to prepare *trans*-4-hydroxyproline by two groups. In each case the starting material was vinyl



SCHEME XXVIII



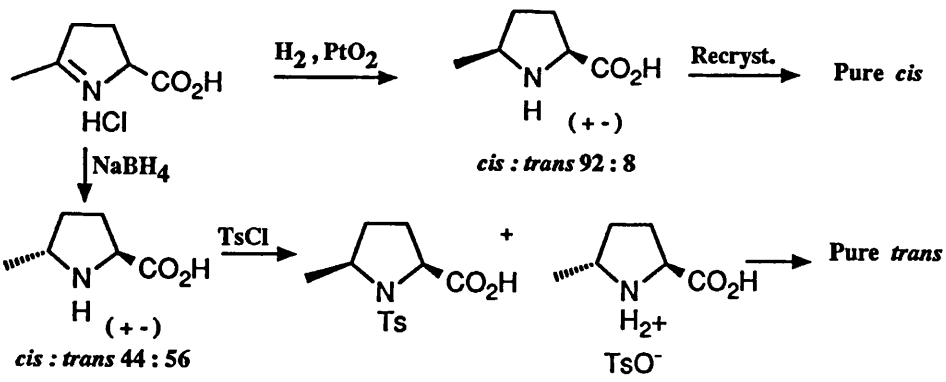
SCHEME XXIX



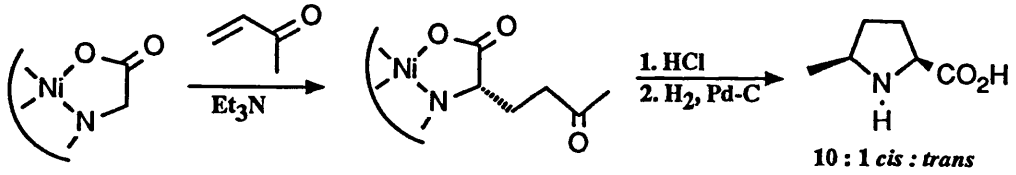
SCHEME XXX

alanine, and the cyclization proceeded in a highly stereoselective fashion[47,48] (Scheme XXVIII). A related approach using thioamides was described recently, and the cyclisation proceeded with up to 14:1 *trans*-selectivity to give a range of 4-substituted proline derivatives including 4-hydroxyproline, 4-aminoproline and various 4-alkylprolines (Scheme XXIX)[49].

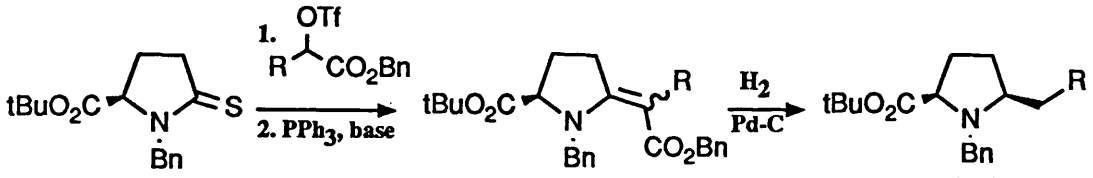
Photolysis of N-chlorohomovaline, as described earlier[16], was used to prepare *cis*- and *trans*-4-methyl proline as a separable mixture (Scheme XXX). Finally, 4-aminoproline was prepared by catalytic hydrogenation of 4-nitropyrrole-2-carboxylic acid[1] and also from 4-hydroxyproline by sequential tosylation, azide displacement and reduction of the azide group[50].



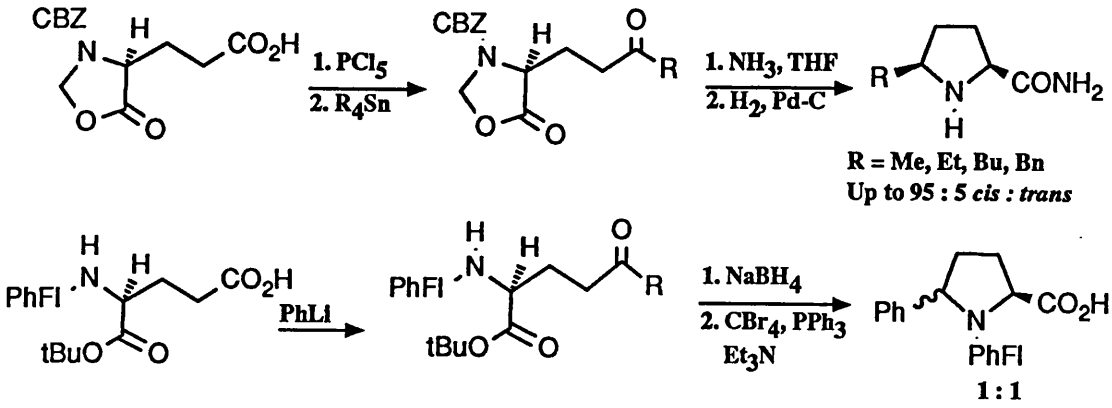
SCHEME XXXI



SCHEME XXXII



SCHEME XXXIII



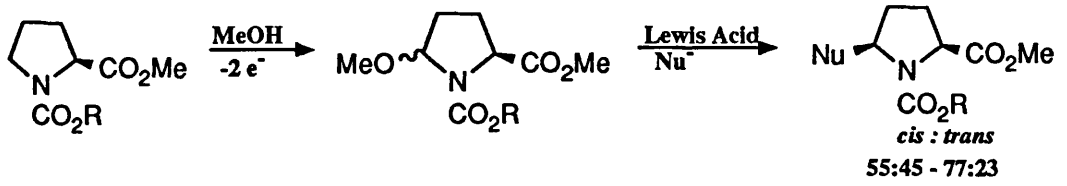
SCHEME XXXIV

Part 5. 5-Substituted Prolines

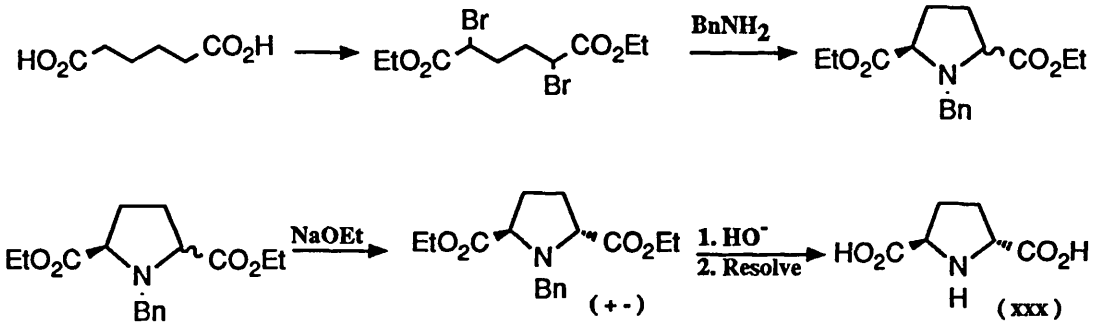
5-Methylproline was originally prepared in 1936 by ammonolysis of 2,5-dibromohexanoic acid, which led to a mixture of diastereomers[51]. A related route was used to prepare 5-propylproline, also as a mixture of diastereomers[29]. An alternative approach which provides scope for control of the relative stereochemistry involves hydrogenation of $\Delta^{1,5}$-pyrroline-2-carboxylic acid derivatives. Early approaches to 5-methyl- and 5-phenylproline using this route gave mixtures of diastereomers[52,53]. However, Overberger *et al* found that hydrogenation using Adam's catalyst gave mostly *cis*-5-methylproline which was obtained in diastereomerically pure form by recrystallization[54]. The same group reported that reduction with sodium borohydride gave a slight excess of *trans*-5-methylproline and they described a means of separating the diastereomers by selective tosylation. Resolution with tartaric acid then gave optically pure products (Scheme XXXI).

Chlorination then rearrangement of 6-phenylpiperidin-2-one furnished a separable mixture of *cis*- and *trans*-5-phenylproline[55]. Reaction of diethyl acetamidomalonate with methyl vinyl ketone followed by reduction gave a mixture of racemic diastereomers of 5-methylproline[52] while Belokon *et al* used their nickel complex to prepare optically active *cis*-5-methylproline[14] (Scheme XXXII).

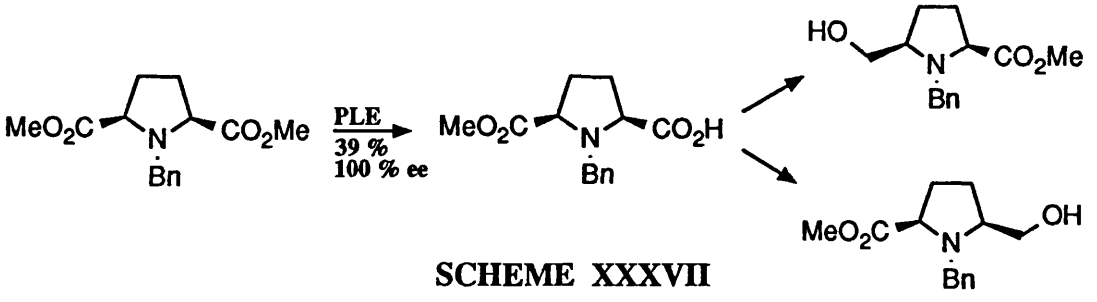
Functionalization of the amide group present in pyroglutamic acid provides a general route to 5-substituted prolines. In 1985 Rapoport reported a synthesis of (+)-anatoxin A, which proceeded *via* the *cis*-5-substituted proline derivative (**xxix**) prepared from pyroglutamic acid[56] (Scheme XXXIII). Ohta *et al* used pyroglutamic acid to prepare a separable mixture of *cis*- and *trans*-5-vinyl proline by controlled addition of vinylmagnesium bromide to the amide group followed by reduction of the resulting ketone then cyclisation[57]. A related approach involving functionalisation of glutamic acid followed by cyclisation was reported by Ho *et al*[58] and subsequently by



SCHEME XXXV



SCHEME XXXVI

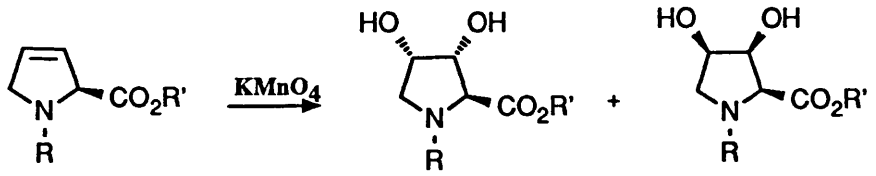


SCHEME XXXVII

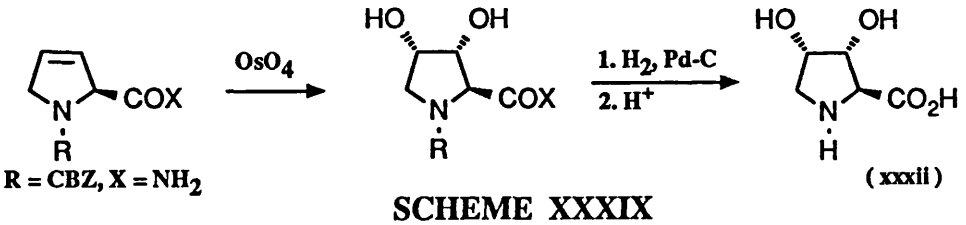
Rapoport[45] (Scheme XXXIV). A more direct approach to the functionalization of proline at C-5, involving alkylation of an N-acylimminium ion, was reported recently[58]. This method avoided the need for a reduction step but the reported yields and diastereoselectivities were moderate (Scheme XXXV).

Trans-pyrrolidine-2,5-dicarboxylic acid (**xxx**) has attracted interest recently as a precursor to the corresponding diol which is a useful chiral auxiliary. A derivative of (**xxx**) was first prepared by Braun and Seemann in 1923, by aminolysis of 2,5-dibromohexane-1,6-dioic acid[59]. This route gave a mixture of diastereomers but it was found later that the *cis*-compound could be epimerized to the *trans*[60], which was then resolved[61] (Scheme XXXVI). Compound (**xxx**) was also prepared from *trans*-5-vinylproline, the preparation of which was described earlier[57].

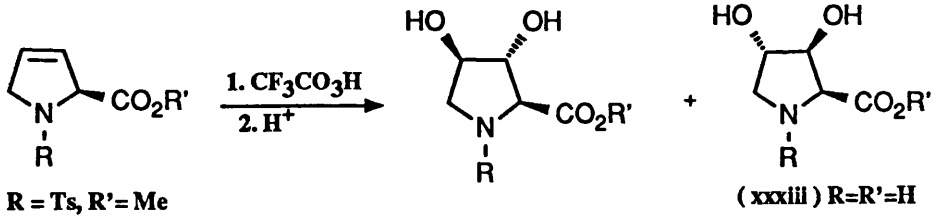
Enzymatic hydrolysis of *cis*-pyrrolidine-2,5-dicarboxylic acid diesters provides a route to optically active derivatives. The first report by Kurichara *et al*[62] was improved by Bjorkling *et al*[63], who found that pig liver esterase hydrolysis of a diester gave optically pure monoester after 39% conversion (Scheme XXXVII).



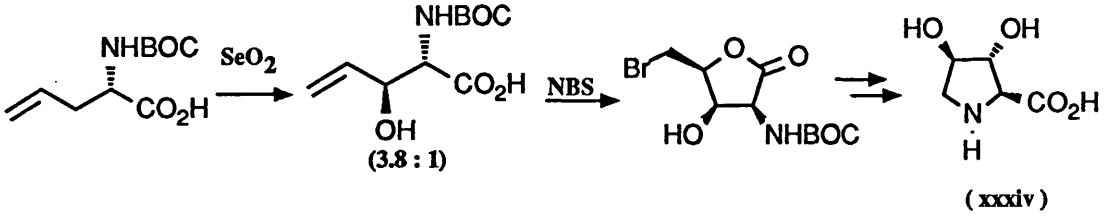
SCHEME XXXVIII



SCHEME XXXIX



SCHEME XL



SCHEME XLI

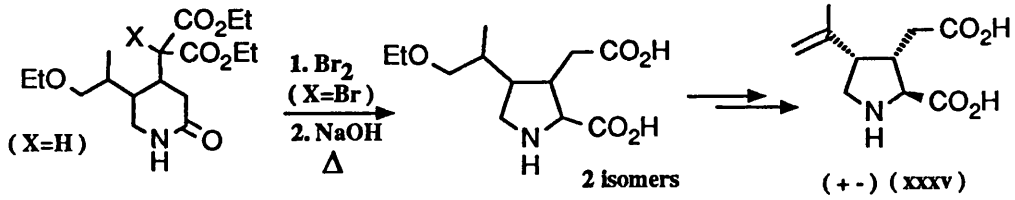
Part 6. Polysubstituted Prolines

(i) 3,4-Dihydroxyproline

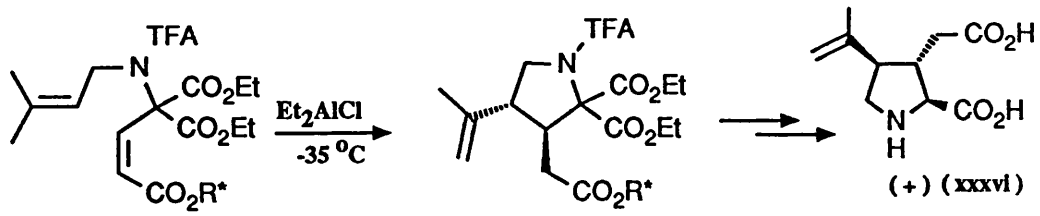
Racemic 2,3-*cis*-3,4-*cis*-dihydroxyproline (**xxxi**) was first prepared by non-selective *cis*-dihydroxylation of 3,4-dehydroproline[64a] (Scheme XXXVIII). Optically active (**xxxi**) was prepared from D-glucose by Fleet *et al*[64b]. The triol which corresponds to the reduced form of (**xxxi**) was prepared by both Fleet and Joullie, who used D-mannose and D-glucose respectively as starting materials[65]. The recent interest in polyhydroxypyrrolidines and piperidines of this type stems from their activity as glycosidase inhibitors which gives them important antiviral activity[66].

Racemic 2,3-*trans*-3,4-*cis*-dihydroxyproline (**xxxii**) was first prepared as described above. The same group found that changing the substituents on the 3,4-dehydroproline nucleus and changing the oxidant led only to (**xxxii**), to the exclusion of (**xxxi**)[64a] (Scheme XXXIX). Optically active (-)-(**xxxii**) was prepared from D-ribose by Fleet *et al*[67] and the corresponding triol has been prepared from D-pyroglutamic acid by two groups[68]. In both cases the reaction sequence involved unsaturation of D-pyroglutamic acid at C3-C4, *cis*-dihydroxylation with osmium tetroxide, then amide reduction.

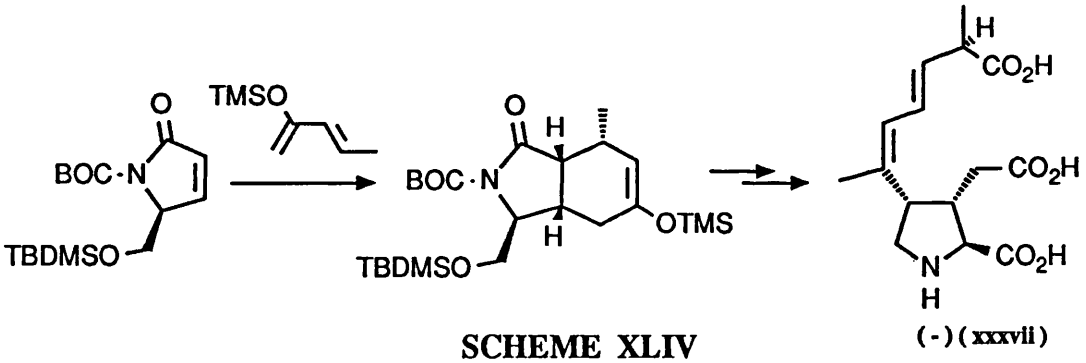
Isolation of 2,3-*cis*-3,4-*trans*-3,4-dihydroxyproline (**xxxiii**) from diatom cell walls in 1969[69] was followed by a synthesis of the racemic material in 1975[70]. The synthesis involved non-selective epoxidation of 3,4-dehydroproline, followed by epoxide opening, which gave a mixture of (**xxxiii**) and the C2-epimer. The synthesis was repeated by a different group using optically active 3,4-dehydroproline which gave, on separation of the diastereomers, optically active (**xxxiii**)[70b] (Scheme XL). The triol which corresponds to (**xxxiii**) has been prepared in both (+)- and (-)- forms from the appropriate enantiomer of arabinose[71]. Other syntheses of this triol involve



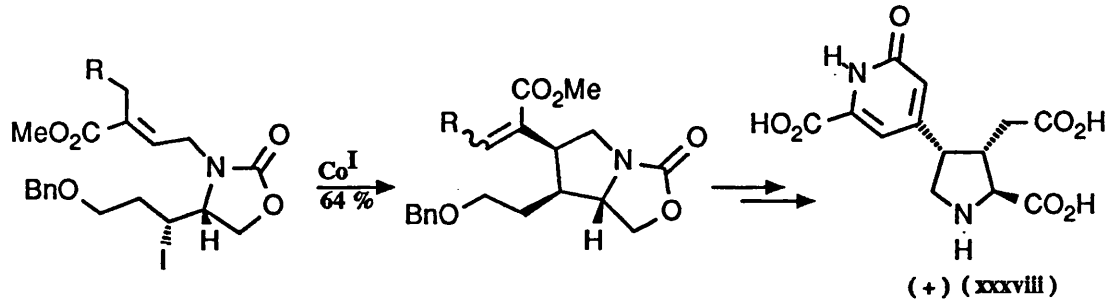
SCHEME XLII



SCHEME XLIII



SCHEME XLIV



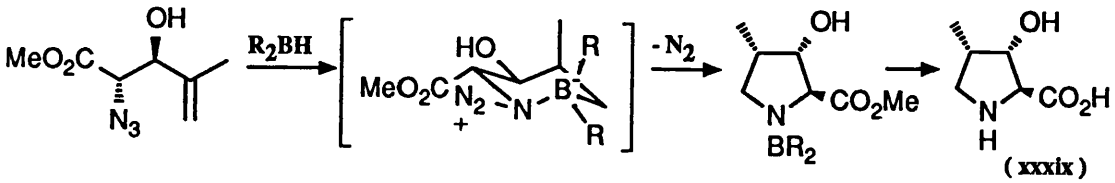
SCHEME XLV

transformation of D-glucose[72a] and triphenylphosphine-induced cyclisation as an azidoepoxide (an intramolecular Staudinger reaction)[72b].

The forth diastereomer, 2,3-*trans*-3,4-*trans*-3,4-dihydroxyproline (**xxxiv**), is also found in nature and was isolated from a toxic mushroom peptide in 1980[73]. The first non-selective synthesis of (**xxxiv**) was described above[70] and was followed by a stereoselective synthesis of optically active (**xxxiv**) by Ohfune in 1985[74] (Scheme XLI). Both (**xxxiv**) and the corresponding triol were prepared from D-glucose by Fleet *et al*[66]. The triol was also prepared from dihydroxyacetone and α-aminoacetaldehyde using the enzyme FDP aldolase to control the stereochemistry of the initial aldol reaction[75].

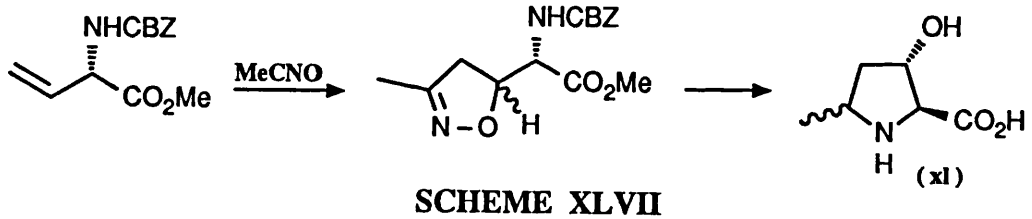
(ii) The kainic acids

The kainic acid family has attracted synthetic effort from a number of groups because of both the biological properties and the synthetic challenge presented by its various members. α-Kainic acid (**xxxv**) was first prepared by Ueno and co-workers in the 1950's, but the various routes used were not stereoselective[76](Scheme (XLII). Oppolzer has used an intramolecular ene reaction to construct the pyrrolidine ring of kainic acids with concurrent control of stereochemistry. This approach culminated in stereoselective syntheses of both (-)-α-kainic acid (**xxxv**) and (+)-α-allokanic acid (**xxxvi**)[77] (Scheme XLIII). Other approaches which focused on construction of the strategic C3-C4 bond of the pyrrolidine ring include an intramolecular radical-alkene cyclisation using cobalt (I)[78], and a highly stereoselective Cope rearrangement[79]. A different approach was used independently by two groups, who employed 1,3-dipolarcycloaddition reactions of azomethine ylides to construct the pyrrolidine ring. Both groups subsequently prepared α-allokainic acid as a (1:1) mixture with the C2-anomer[80].



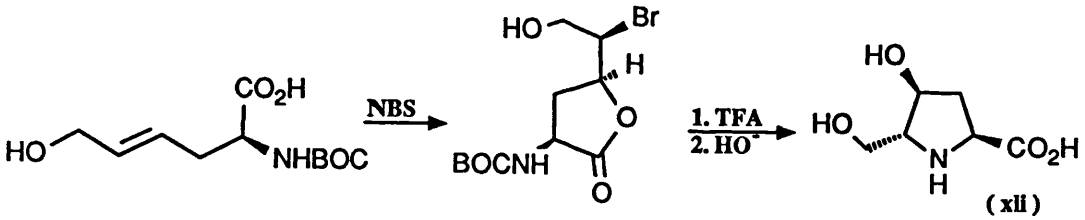
(xxxix)

SCHEME XLVI



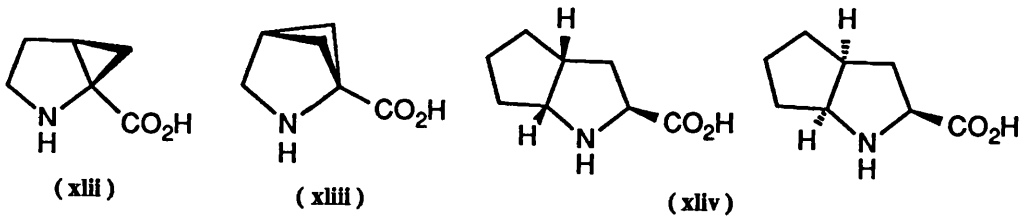
(xl)

SCHEME XLVII



(xli)

SCHEME XLVIII



(xlii) (xliii) (xliv)

SCHEME XLIX

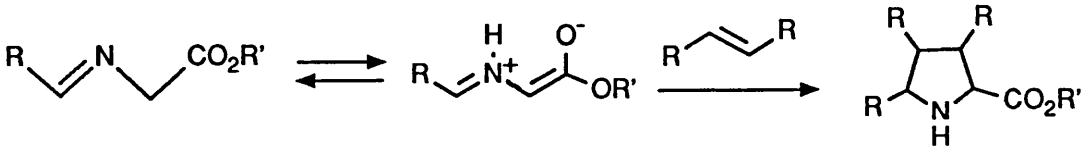
Another member of the kainic acid group is domoic acid (**xxxvii**). The first total synthesis and proof of structure was reported by Ohfune in 1982, who prepared (-)-domoic acid using a Diels-Alder reaction to control the stereochemistry[81] (Scheme XLIV). Ohfune has also prepared (+)-acromelic acid A (**xxxviii**) from (-)-α-kainic acid. Other syntheses of (+)-acromelic acid A have exploited an intramolecular azomethine ylide cycloadditon and an intramolecular radical cyclisation[78b, 82] (Scheme XLV). Acromelic acid B, which differs from acromelic acid A only in the structure of the pyridone residue, has been prepared in optically active form from (-)-α-kainic acid by Matsumoto[83].

(iii) Other disubstituted prolines

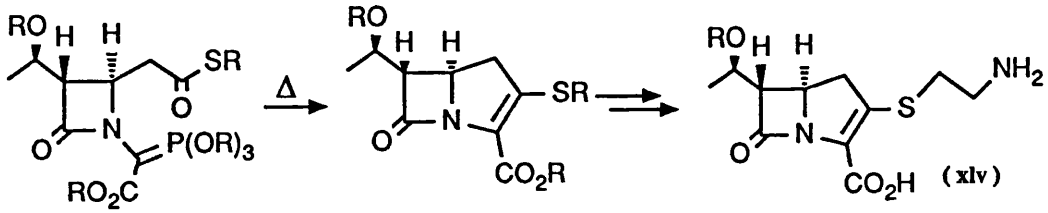
The synthesis of (2S, 3S, 4S)-3-hydroxy-4-methyl proline (**xxxix**) has been reported by three groups. This proline derivative is found in the natural product echinocandin and was first prepared by Ohfune in 1986 using established methodology to control the stereochemistry[84]. Evans used an unusual borane-mediated azide decompositon to construct the pyrrolidine ring of (**xxxix**) (Scheme XLVI) and the third synthesis of (**xxxix**) by Mulzer *et al* exploited an intramolecular Staudinger reaction. A related compound, 3-methyl-4-oxoproline, was prepared by a hetero-Diels Alder reaction[85].

3-Hydroxy-5-methylproline (**xl**) was first prepared as a mixture of all four diastereomers. A later synthesis by Nozoe *et al*, based on a nitrile oxide cycloaddition reaction, allowed control of two of the three chiral centres of (**xl**)[86] (Scheme XLVII). Bulgecinine (**xli**) is a constituent of the natural product bulgecin and has been prepared in optically active form by four groups[87]. The most direct of these syntheses exploits a bromolactonization to control the relative stereochemistry (Scheme XLVIII).

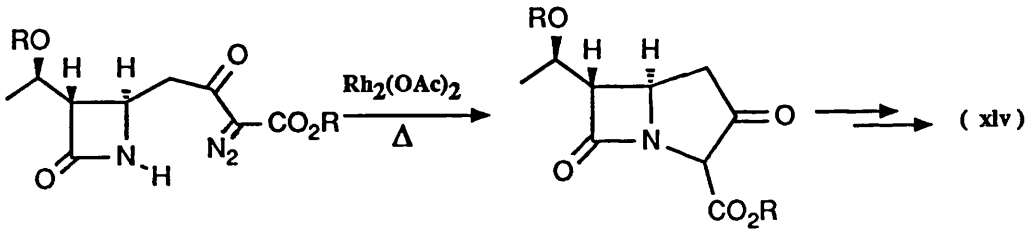
Bridged bicyclic proline derivatives are of interest when studying



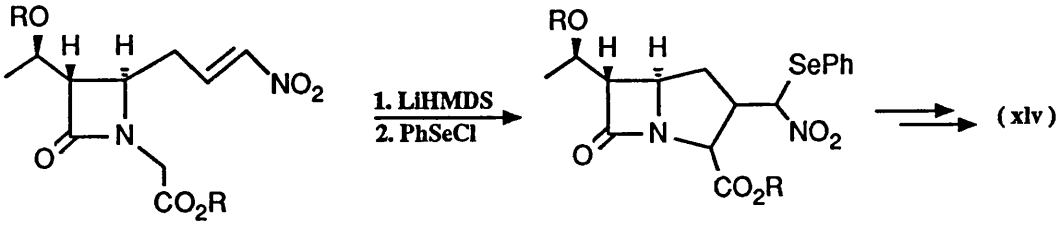
SCHEME L



SCHEME LI



SCHEME LII



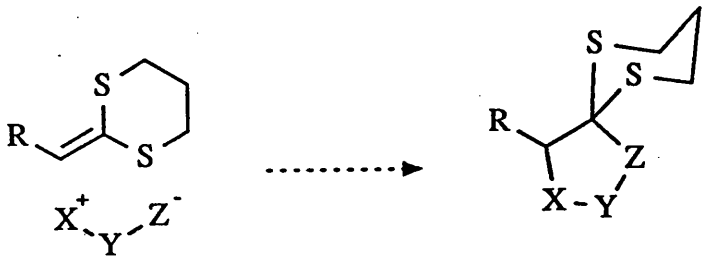
SCHEME LIII

structure-activity relationships because they restrict the number of conformations available to the pyrrolidine ring. 2,3-Methanoproline (**xlii**) was prepared by treatment of 2,3-dehydroproline with diazomethane,[88] 2,4-methanoproline (**xliii**) was prepared by an intramolecular photochemical [2+2] cycloaddition[89] and both diastereomers of 2-azabicyclo[3.3.0]octane-3-carboxylic acid (**xliv**) were prepared by an intramolecular radical cyclisation[90] (Scheme XLIX).

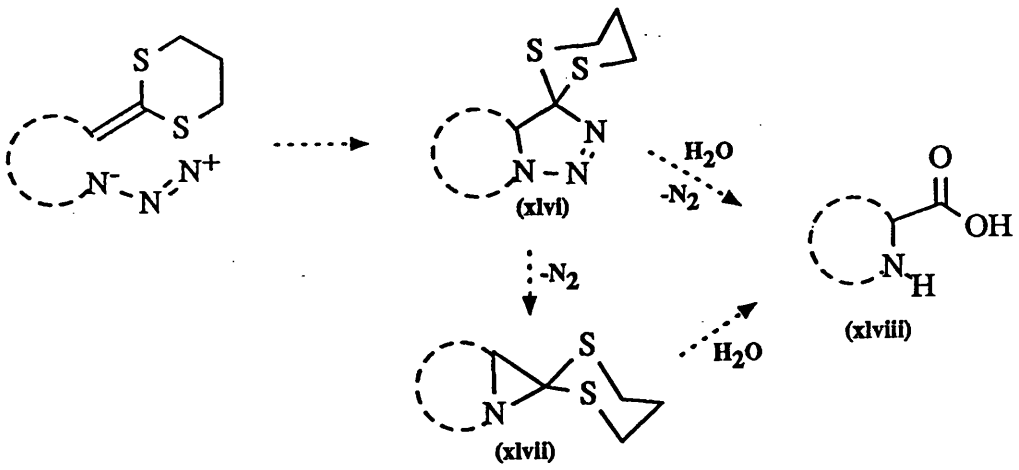
(iv) Polysubstituted Prolines

Cycloaddition reactions of azomethine ylides provide, as mentioned above, a convenient route to pyrrolidines. Generation of azomethine ylides by a [1,2] prototropic shift was discovered independently by three groups in 1978-9[91] (Scheme L). A wide variety of substituents on the 1,3-dipole and the dipolarophile has led to the synthesis of a large number of polysubstituted prolines and the reaction has been reviewed[92]. Two of the three original reporters continue to publish in this area[93].

Finally, a brief mention will be given to the synthesis of carbapenems, which contain the proline nucleus. The biological (and hence commercial) importance of this class of compounds has led to an intense synthetic effort, in particular towards thienamycin (**xlv**) which has attracted over twenty total syntheses. Two of the most frequently used routes are an intramolecular Wittig-type reaction[94] (Scheme LI) and a carbene insertion[95] (Scheme LII). New methods for the synthesis of (**xlv**) continue to be published, including a recent report by Hanessian *et al* in which formation of the C2-C3 bond of the proline nucleus was the key step[96] (Scheme LIII).



SCHEME LIV



SCHEME LV

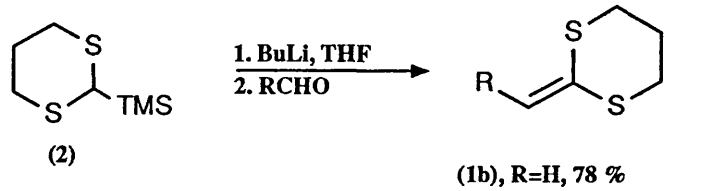
Part 7. Introduction to the Results and Discussion.

Our own approach to the synthesis of cyclic amino acids forms a major part of the work described in this thesis and stems from a general interest in the chemistry of ketene thioacetals. More particularly, we wanted to investigate the reactivity towards 1,3-dipoles of the C-C double bond present in ketene thioacetals. Diels Alder[97] and [2+2][98] cycloaddition reactions are known, and a general review of the chemistry of ketene thioacetals was published by Kolb in 1980, then updated in 1990[99].

A schematic 1,3-dipolarcycloaddition reaction of ketene thioacetals is shown in scheme LIV. More specifically, scheme LV shows our proposed intramolecular variant of this reaction in which the 1,3-dipole is an azide. The triazoline cycloadduct **(xlvi)** shown in this scheme is interesting because in carrying out the cycloaddition reaction (albeit on paper) we have constructed a new nitrogen heterocycle and have also maintained the masked carboxylic acid function which was originally present in the ketene thioacetal. Hydrolysis of the triazoline **(xlvi)**, or the corresponding aziridine **(xlvii)**, would then furnish the cyclic amino acid **(xlviii)**. With this transformation in mind, we began our investigation of ketene thioacetals as 1,3-dipolarophiles by investigating their reactivity towards electron-deficient azides, and the outcome of these initial intermolecular reactions is described in chapter 1. Shortly after beginning this work, a report describing nitrile oxide and nitrone cycloaddition reactions with ketene thioacetal (**1b**) appeared[181]. This was followed by a publication by Junjappa and co-workers who described the reaction between sodium azide and α-oxoketene thioacetals, which was also thought to involve 1,3-dipolarcycloaddition[100].

RESULTS AND DISCUSSION

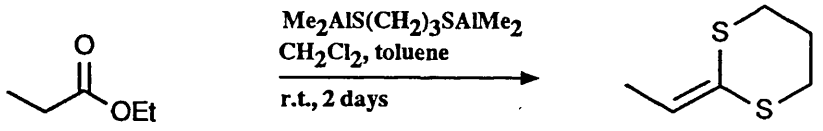
CHAPTER 1



(2)

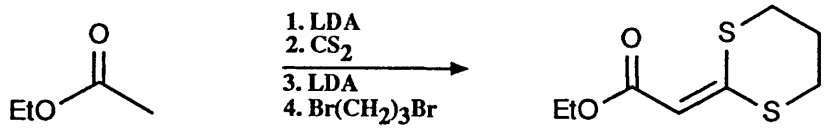
(1b), R=H, 78 %
(1d), R=Ph, 90 %
(1e), R=2-Furanyl, 66 %

SCHEME 1.



(1c), 40 %

SCHEME 2.



(1a), 37 %

SCHEME 3.

CHAPTER 1

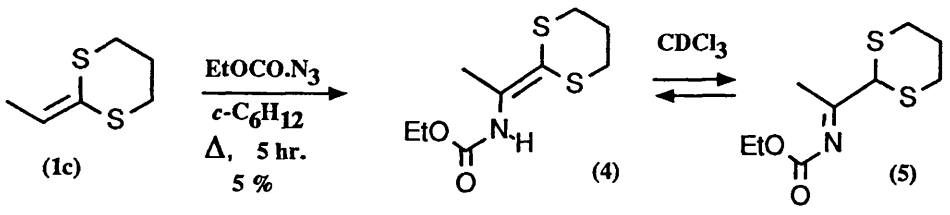
Intermolecular Reactions of Ketene Thioacetals with Electron Deficient Azides

Part 1. Synthesis of Ketene thioacetals

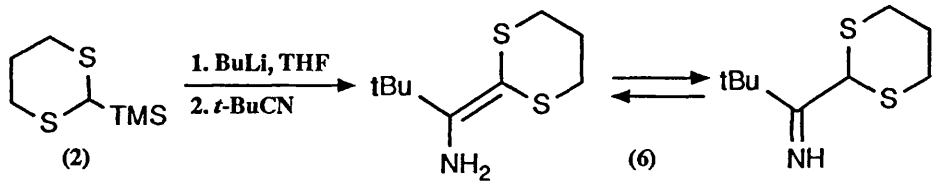
As outlined in the introduction, we decided to begin our program by studying the intermolecular reactivity of ketene thioacetals towards electron-deficient azides. For this study, we needed a range of ketene thioacetals and five substrates (**1a-e**) were prepared. These ketene thioacetals have C-2 substituents which possess a variety of electronic properties from electron-withdrawing (**1a**, R=CO_2Et) through the relatively neutral groups (**1b**, R=H, **1c**, R=Me) to electron donating (**1d**, R=Ph, **1e**, R=2-furanyl). Compounds (**1a-e**) were prepared either by following literature procedures or by adapting known methods.

2-Methylene-1,3-dithiane (**1b**) (R=H) was prepared by Peterson olefination of formaldehyde using 2-trimethylsilyl-1,3-dithiane (**2**)[101] (Scheme 1). Best results were obtained when paraformaldehyde was added as a suspension in THF to the anion of (**2**). Compounds (**1d**)[101] and (**1e**)[102] were also prepared by Peterson olefination using the anion of (**2**) and a solution in THF of benzaldehyde or furfural respectively. These reactions all proceeded in good yield.

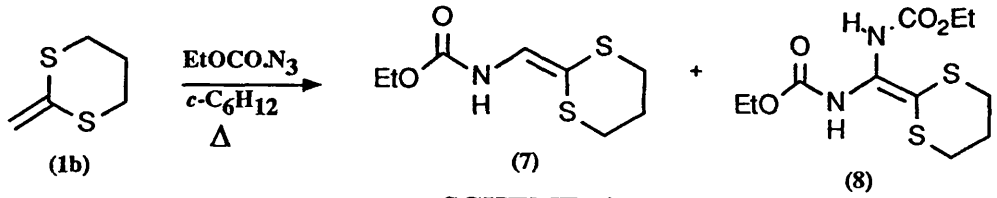
In 1973 Corey and Beams introduced a reagent for protecting esters and lactones as ketene thioacetals[103]. This reagent, bis(dimethylaluminium)propane-1,3-dithiolate (BDP), was prepared from propane-1,3-dithiol and trimethylaluminium, and we have used it extensively to prepare ketene thioacetals, including (**1c**) which was prepared from ethyl propionate. (Scheme 2). Finally, the electron deficient ketene thioacetal



SCHEME 4.



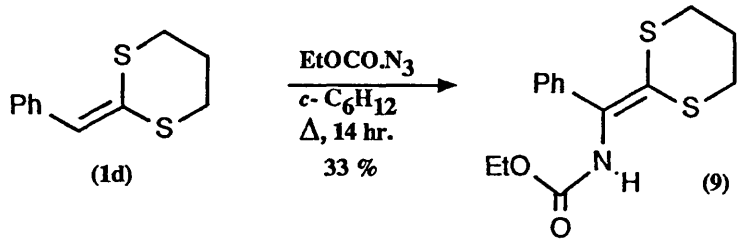
SCHEME 5.



SCHEME 6.

TABLE 1.

Equiv. Azide	Time	Yield(7)	Yield(8)
2	11 hr	10.8 %	20.2 %
10	3 hr	8.9 %	29 %



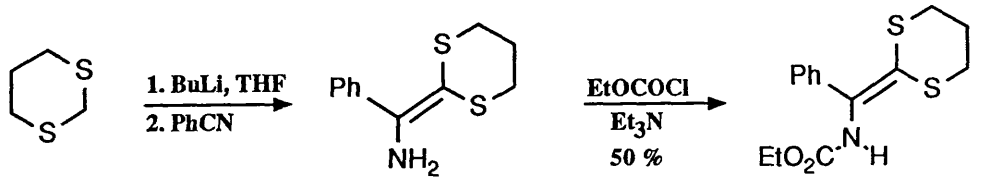
SCHEME 7.

(**1a**) was prepared by condensation of ethyl acetate, carbon disulphide and 1,3-dibromopropane using a variation of the method reported by Dieter[104] (Scheme 3).

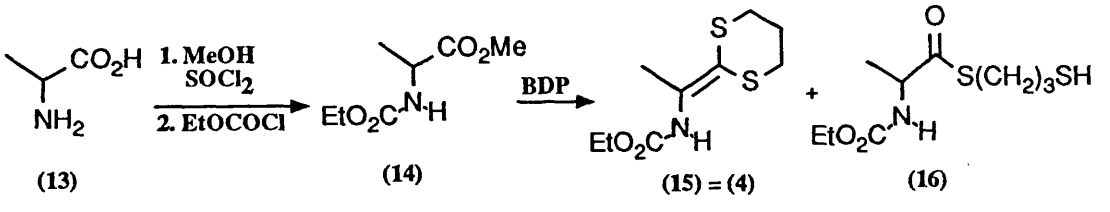
Part 2. Reaction of Ketene thioacetals (1a-e) with ethyl azidoformate

Ethyl azidoformate (**3**)[105] was prepared from ethyl chloroformate and activated sodium azide[106]. In a typical experiment, a mixture of (**3**) and ketene thioacetal (**1**) was dissolved in cyclohexane and heated at reflux under an atmosphere of nitrogen. The reaction mixture was monitored by TLC for loss of (**1**), and further additions of azide (**3**) were made if necessary. Initial attempts to perform the reaction in toluene or decalin led to adducts of the azide (**3**) and solvent[107]. The first successful reaction was between (**1c**, R=Me) and ethyl azidoformate (**3**). After heating for 5 hours, the major product was isolated in 5% yield and assigned structure (**4**) (Scheme 4). The product was unstable in deuterochloroform and was thought to exist in equilibrium with tautomer (**5**) (ratio approx. 1:1), as judged by the appearance of new signals in the ^{1}H NMR spectrum on standing in deuterochloroform. A similar tautomerism has been reported by Page *et al* for the related α-aminoketene thioacetal (**6**), prepared from tert-butyl cyanide and the dithiane derivative (**2**) (Scheme 5)[108].

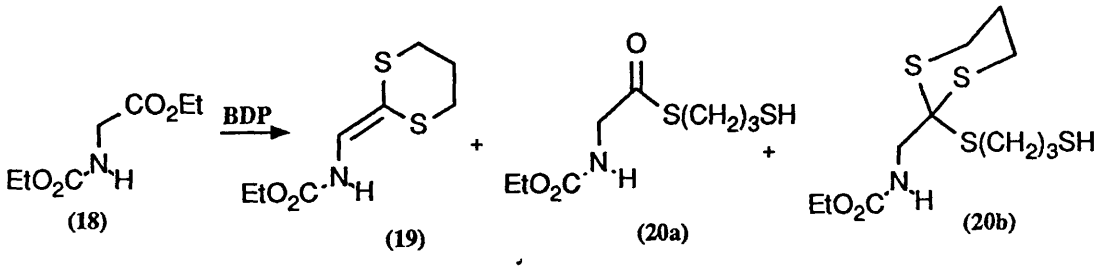
2-Methylene-1,3-dithiane (**1b**) reacted with ethyl azidoformate (**3**) in a similar fashion to (**1c**) to give aminoketene thioacetal (**7**) (Scheme 6). In addition, a 2:1 adduct (**8**) was produced on prolonged heating. The relative amounts of this product and the (1:1) adduct (**7**) depended on the amount of azide present and on the reaction time (Table 1). Ketene thioacetal (**1d**) gave only the 1:1 adduct (**9**), in 33% yield, after refluxing for 14 hours (Scheme 7). On prolonged heating with ethyl azidoformate (**3**), the 2-furanyl derivative (**1e**) gave a complex mixture of products which were not identified. In contrast, the 2-ethoxycarbonyl derivative (**1a**) proved completely unreactive towards (**3**) under these conditions.



SCHEME 8.



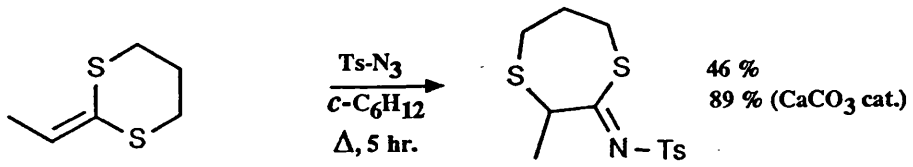
SCHEME 9.



SCHEME 10.

In order to confirm the structure of cycloaddition products (**4**), (**7**) and (**9**), which are all α-aminoketene thioacetals, an alternative synthesis of these compounds was required. The phenyl derivative (**9**) was prepared by acylation of the closely related compound (**10**). Addition of 2-lithio-1,3-dithiane (**11**) to benzonitrile followed by chromatography gave (**10**), as reported by Page *et al.*[108] Treatment of (**10**) with ethyl chloroformate and triethylamine gave the N-ethoxycarbonyl derivative (**12**), whose spectroscopic data were identical to those of (**9**) (Scheme 8). Unfortunately, this route to α-aminoketene thioacetals is not generally applicable since it is limited to nitriles which do not possess α-hydrogen atoms. Attempted addition of 2-lithio-1,3-dithiane (pK_A of dithiane = 39)[109] to acetonitrile (pK_A = 31.3) gave none of the desired α-aminoketene thioacetal. The major product isolated from this reaction was thought to be polymeric acetonitrile resulting from deprotonation of acetonitrile by 2-lithio-1,3-dithiane. For this reason, an alternative route to α-aminoketene thioacetals was sought, in order to confirm the structures of (**4**) and (**7**). The starting point for the synthesis of (**4**) was alanine (**13**), which was protected as the carbamate-ester derivative (**14**) (Scheme 9). Treatment of (**14**) with BDP gave, after 2 days at room temperature, 5% of the desired aminoketene thioacetal (**15**) whose spectral data were identical to those of compound (**4**). In addition to product (**15**), the thioloester (**16**) was also isolated in 23% yield. The isolation of this intermediate is not normally encountered in the conversion of esters to ketene thioacetals and may reflect the increase in steric bulk at C_α, or the decreased acidity of the α-proton. By analogy, the derivative (**17**) of the amino acid glycine was converted to carbamate-ester (**18**) which, on treatment with BDP, gave 17% of aminoketene thioacetal (**19**) (Scheme 10). Compound (**19**) proved to be spectroscopically identical to (**7**), thus confirming the structure. In addition the thioloester (**20a**) was produced in 10% yield and the trithioorthoester (**20b**) was isolated in 11% yield.

In summary, ketene thioacetals (**1b, c and d**) reacted with ethyl azidoformate to



(1c) (22)

SCHEME 11.

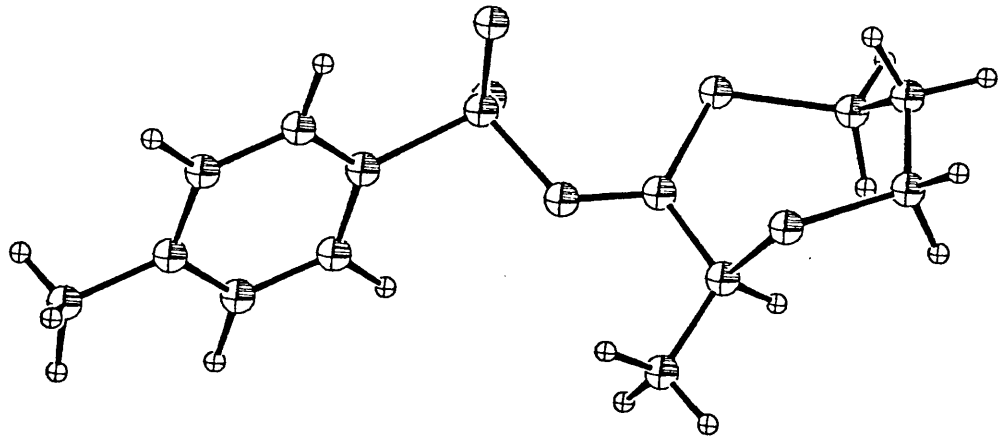
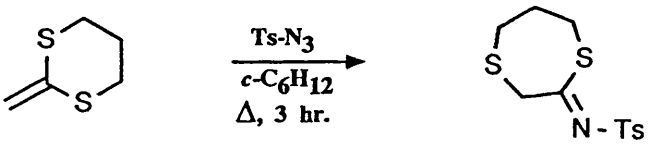
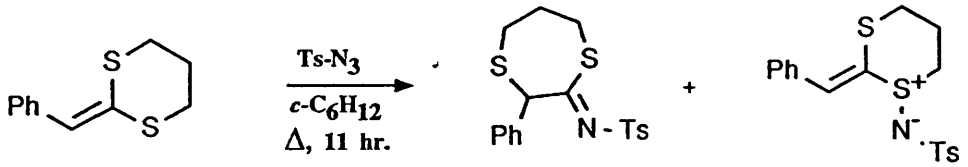


Figure 1., ORTEP drawing of (22)



(1b) (23), 59 %

SCHEME 12.



(1d) (24), 24 % (25), 18 %

SCHEME 13.

produce α-aminoketene thioacetals in low yield, and the structures of the three cycloadducts were confirmed by alternative syntheses.

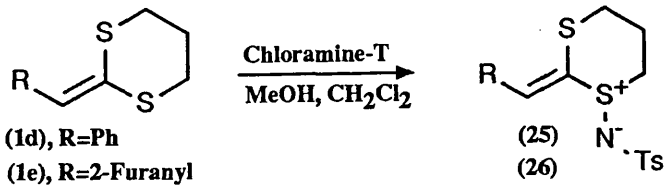
The conversion of α-amino acid derivatives to α-aminoketene thioacetals is noteworthy since the latter represents a masked version of the former. The reverse process, i.e. conversion of α-aminoketene thioacetals to α-amino acids will be discussed later, as will the synthetic potential of this process.

Part 3. Reaction of Ketene Thioacetals with Tosyl Azide

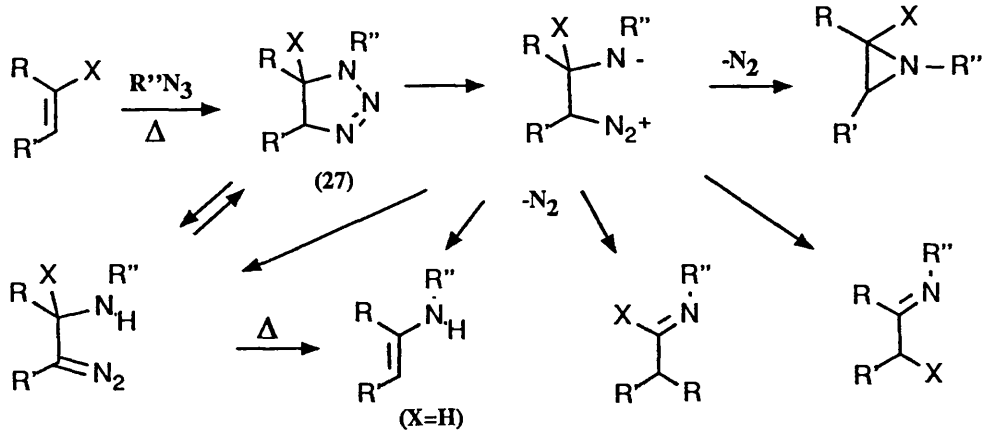
Tosyl azide (**21**) was prepared from tosyl chloride and sodium azide[110], and was subjected to the same series of reactions as ethyl azidoformate using ketene thioacetals (**1a-e**). In a typical experiment, the starting materials were dissolved in cyclohexane and heated at reflux under an atmosphere of nitrogen. The progress of the reaction was monitored by TLC and further equivalents of azide were added, if necessary. The reaction was first performed using the methyl derivative (**1c**) which, after 5 hours at reflux in the presence of tosyl azide (**21**), gave the ring expanded product (**22**) in 46% yield (Scheme 11). Both the yield of the product and the rate of the reaction were increased by the addition of catalytic amounts of calcium carbonate, triethylamine or *p*-toluene sulphonic acid, and with calcium carbonate as catalyst the yield of (22) was 89%. The product (**22**) was recrystallised from methanol and the structure of (**22**) was confirmed by X-ray crystallographic analysis[111] (Fig. 1).

Ketene thioacetal (**1b**) reacted with tosyl azide (**21**) to give the analogous product (**23**) in 59% yield (Scheme 12). The structure was assigned by comparison of ^{1}H NMR and mass spectra with those of compound (**22**).

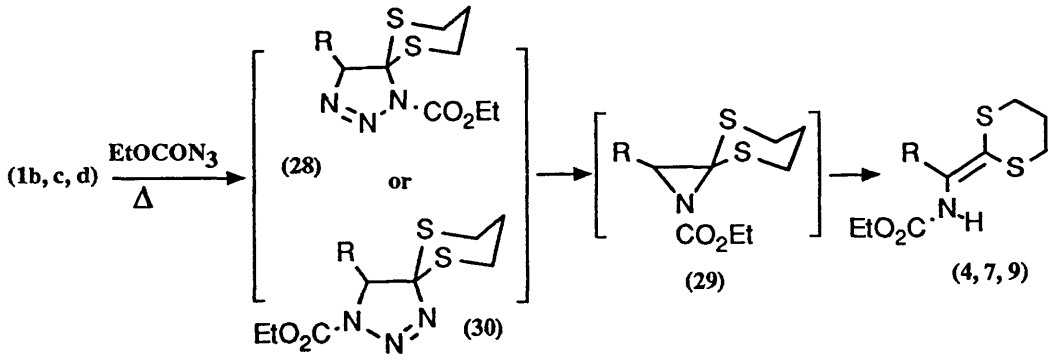
The phenyl derivative (**1d**) gave the dithiepane (**24**) in 24% yield, by analogy with products (**22**) and (**23**). In addition, the sulphilamine (**25**) was formed in 18%



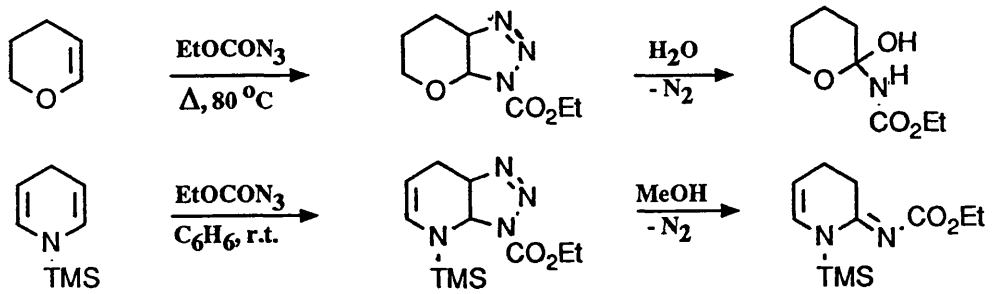
SCHEME 14.



SCHEME 15.



SCHEME 16.



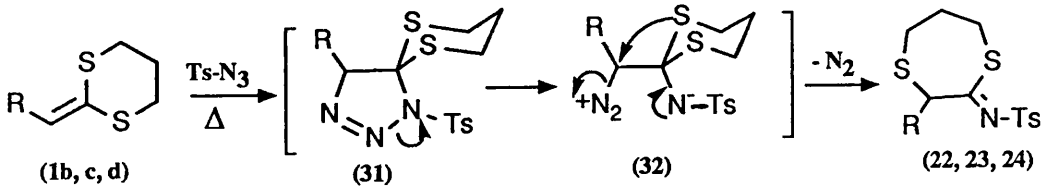
SCHEME 17.

yield (Scheme 13). The related sulphilamine (**26**) was the only product isolated (25% yield) when 2-furanyl derivative (**1e**) was heated with tosyl azide for 19 hours. The isolation of adduct (**26**) contrasts the reaction of (**1e**) with ethyl azidoformate which gave no isolable products. Authentic samples of sulphilimines (**25**) and (**26**) were prepared by treating the parent ketene thioacetals (**1d**) and (**1e**) respectively with chloramine-T[112] (Scheme 14). As with ethyl azidoformate, the ethoxycarbonyl derivative (**1a**) proved unreactive towards tosyl azide, even after prolonged reaction times.

Part 4. Discussion of the mechanism of the intermolecular reaction

Organic azides react with olefins by 1,3-dipolar cycloaddition to form triazolines (**27**), as first reported by Wolff in 1912[113]. Strongly electron withdrawing substituents on the azide (CN, CO_2R, CO.Ar, SO_nAr, n = 1,2)facilitate addition to relatively electron rich alkenes but render the resulting triazolines unstable with respect to loss of nitrogen[114]. The final product is then determined by subsequent reaction of the intermediate betaines so formed (Scheme 15).

The formation of α-aminoketene thioacetals (**4**, **7** and **9**) from ketene thioacetals and ethyl azidoformate can be explained by initial 1,3-dipolar cycloaddition to give triazoline (**28**) which decomposes with loss of nitrogen to give to aziridine (**29**). This aziridine in turn rearranges to give the observed products (Scheme 16). The regiochemistry of the dipolar cycloaddition reaction can be explained by electronic considerations (i.e. the direction of polarisation of azide and ketene thioacetal) and is consistent with the products previously reported from the reaction of ethyl azidoformate with O- and N- substituted alkenes[115,116] (Scheme 17). However, two other explanations for the outcome of the reaction can be offered. The first alternative explanation is that the regiochemistry of cycloaddition is reversed (Scheme 16). The initial triazoline (**30**) would then decompose to give the same aziridine (**29**). This



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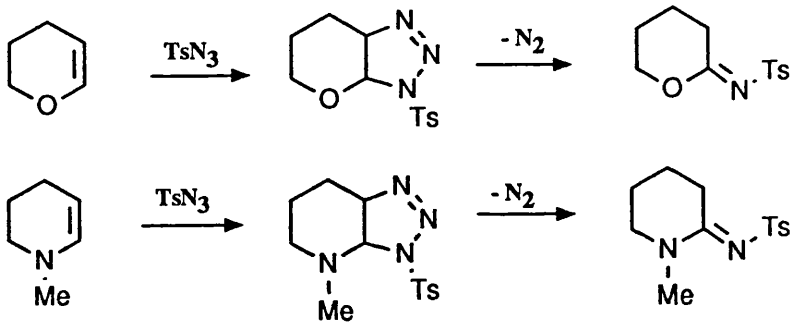
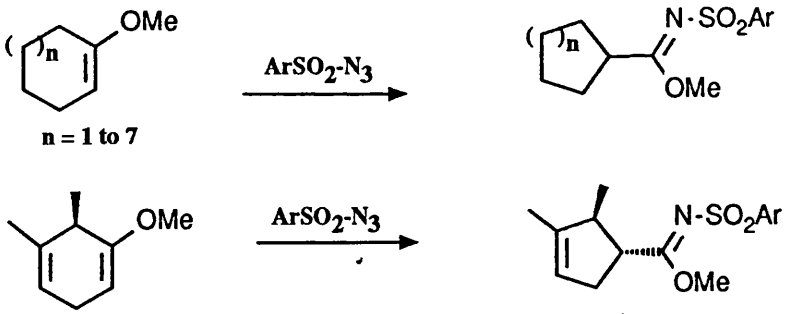


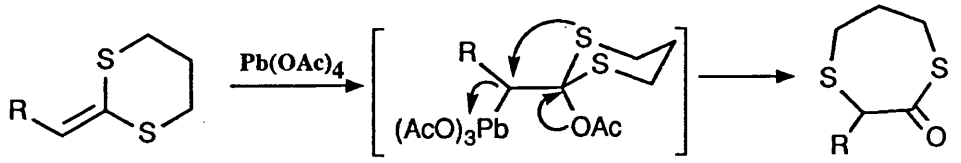
SCHEME 19.



SCHEME 20.

regiochemistry is favoured sterically and overcomes the need to explain the absence of sulphur migration in the rearrangement of triazoline (**28**) (*vide infra*). The second alternative explanation is that the azide decomposes to give the corresponding nitrene, which adds to the double bond of the ketene thioacetal to give aziridine (**29**) directly. While this latter route cannot be completely excluded, it is thought to be less likely because previous work has shown that ethyl azidoformate undergoes 1,3-dipolar cycloaddition at 80°C some 20 times faster than it decomposes (as judged by the rate of evolution of nitrogen in the presence and absence of dipolarophile)[115]. Thus the α-aminoketene thioacetals (**4**, **7** and **9**) probably arise from 1,3-dipolar cycloaddition of ethyl azidoformate to ketene thioacetals (**1b**, **c** and **d**), followed by decomposition of the resulting triazolines.

Aryl sulphonyl azides such as tosyl azide undergo 1,3-dipolar cyloaddition reactions with electron rich alkenes, in a similar fashion to ethyl azidoformate[117,118]. The formation of adducts (**22**), (**23**) and (**24**) from ketene thioacetals (**1b**, **c** and **d**) can be explained in terms of 1,3-dipolar cycloaddition to give triazoline (**31**), followed by fragmentation and rearrangement of betaine (**32**) (Scheme 18), although direct rearrangement of (**31**) to the isolated products is also possible[119]. Rearrangement of triazolines to give imines is well documented in the literature; enamines and enol ethers bearing hydrogen at C-α underwent 1,3-dipolar cycloaddition followed by decomposition and hydrogen migration when treated with aryl sulphonyl azides (Scheme 19)[119,120]. Enol ethers bearing alkyl groups at C_α underwent alkyl migration which, in the case of cyclic enol ethers, led to ring contraction (Scheme 20)[121]. Since the literature contains a large number of reports on 1,2-sulphur migration[122,123], the ring expansion which accompanies decomposition of triazoline (**31**) is unremarkable. Indeed, betaine (**32**) is ideally set up for such a migration, having a good leaving group adjacent to a carbon-sulphur bond, in addition to a strongly electron donating group to assist the migration of sulphur. A closely related oxidative ring expansion of ketene thioacetals has been reported, and again the



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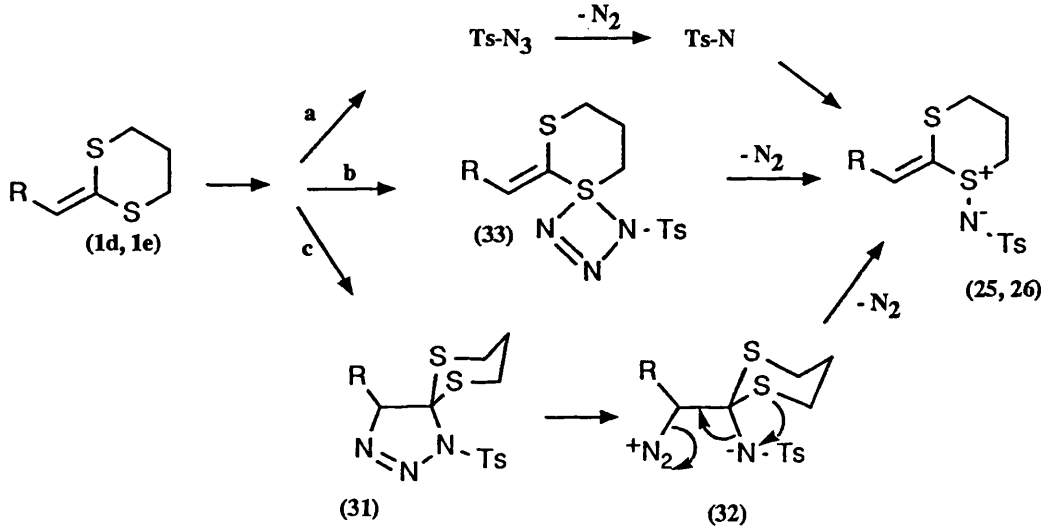

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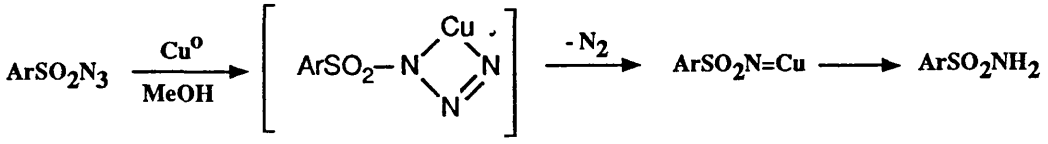


SCHEME 23.

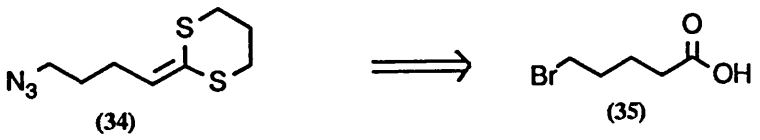
proposed intermediate was ideally set up to undergo sulphur migration (Scheme 21)[123].

The formation of sulphilimines (**25**) and (**26**) from tosyl azide and ketene thioacetals (**1d, 1e**) may occur in one of three ways. Firstly, tosyl azide may decompose, when heated, to produce tosyl nitrene which is captured by sulphur as it forms. (Scheme 22, path a). However, this is unlikely since the decomposition temperature of sulphonyl azides is reported to be 120-150°C[114] but the reaction was performed in refluxing cyclohexane (b.p. 80-81°C), and sulphilimines are known to be unstable at the temperatures required to decompose azides[128]. The second proposed mechanism for formation of sulphilimines (**25**) and (**26**) involves direct attack on the azide by sulphur, to produce the intermediate (**33**) which can then lose nitrogen to give the sulphilimine (Scheme 22, path b). A related intermediate has been proposed in the decomposition of aryl sulphonyl azides by copper metal (Scheme 23)[125]. The formation of sulphilimines only from ketene thioacetals (**1d, 1e**) which have electron-donating C-2 substituents, is explained by the enhanced electron density, and hence nucleophilicity, at sulphur. The third suggested mechanism involves 1,3-dipolar cycloaddition to give triazoline (**31**) which rearranges to give betaine (**32**) (Scheme 22, path c). Rather than rearranging to give dithiepane derivatives (**22**), (**23**) and (**24**), an alternative outcome is migration of nitrogen from carbon to sulphur, which can be regarded as a nitrene migration. The electron-donating substituents of the ketene thioacetal may stabilise the developing positive charge at C-2 to the extent that this pathway competes with sulphur migration (R = Ph) or replaces it (R = 2-furanyl).

Where more than one mechanism has been put forward for formation of products, it is not possible to say that one of these will be correct and the others wrong. Further experimentation would be required in order to unequivocally identify the principle mechanistic pathways involved. In spite of this, it is interesting to

speculate that all three products (i.e. α-aminoketene thioacetals, 2-imino-1,4-dithiepanes and sulphilimines) may arise from a common intermediate, namely betaine (**32**).

CHAPTER 2



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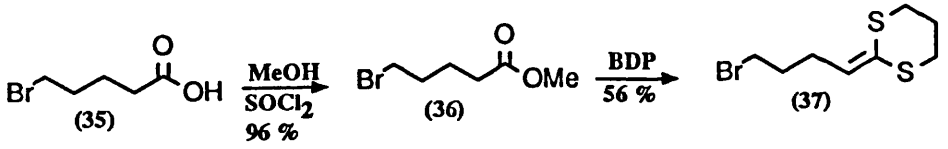

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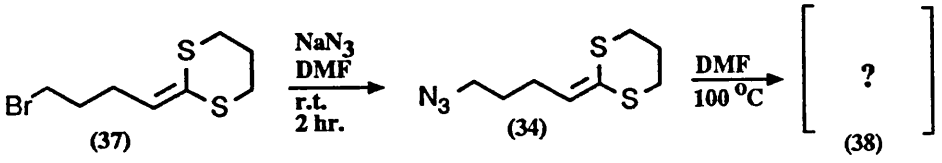

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CHAPTER 2

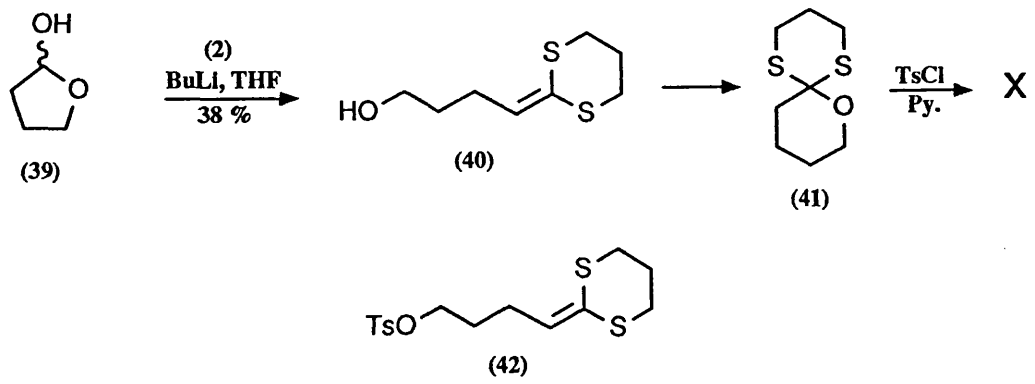
The Intramolecular Ketene Thioacetal-Azide Cycloaddition Reaction and its Application to the Synthesis of Proline

Part 1. Synthesis of an appropriate cyclisation precursor

Wishing to extend the reactions described in Chapter 1 to the intramolecular variant, we required a synthesis of the starting material (**34**) which contains both the azide and ketene thioacetal functional groups linked by a hydrocarbon chain. The availability of 5-bromovaleric acid (**35**) and its homologues makes this an obvious choice as a precursor to (**34**) (Scheme 24).

Our first approach to (**34**) was to install the ketene thioacetal functionality before introducing the azide. Esterification of (**35**) using thionyl chloride and methanol[126] provided the bromo ester (**36**) in high yield. Treatment of (**36**) with BDP then gave the corresponding ketene thioacetal (**37**) in 56% yield (Scheme 25). Compound (**37**) was not stable, but could nevertheless be converted to the desired azide (**34**) simply by stirring with sodium azide in DMF. This solution of (**34**) in DMF was then heated under reflux and the temperature of the reaction mixture was steadily increased. At 95°C a new product was observed by TLC. After heating for 5 hours at 100°C (oil bath temperature) both (**34**) and the new product (**38**) where present in approximately equal amounts (Scheme 26). We attempted to isolate the two products by column chromatography but ^{1}H NMR spectra of both (**34**) and (**38**) showed that decomposition had taken place. The structure of compound (**38**) was subsequently established, but proved elusive for quite some time after this first thermolysis experiment.

The instability of ω-bromo ketene thioacetal (**37**) called for a different



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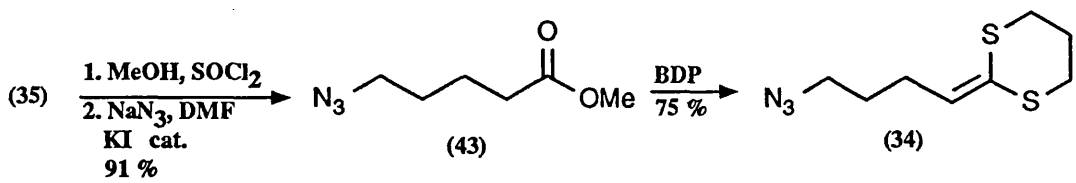
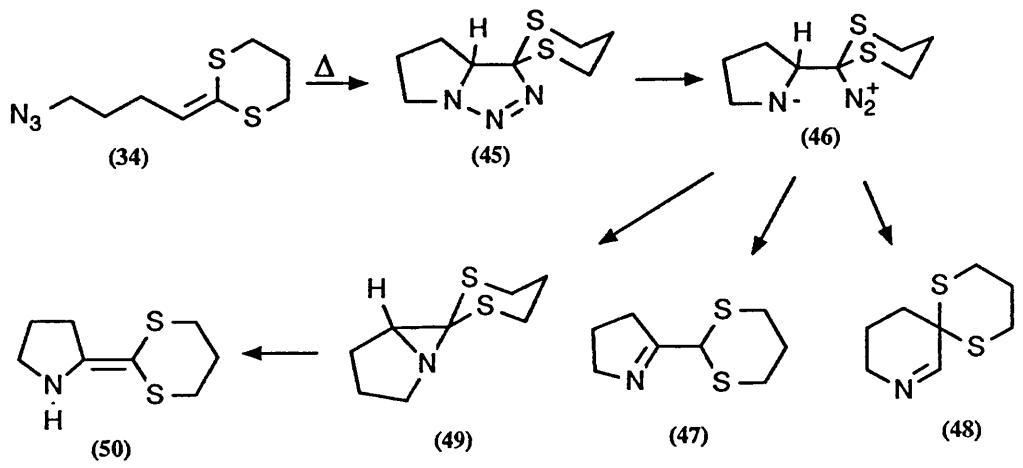


SCHEME 28.

method of introducing the azide group and, to this end, a synthesis of tosylate (**42**) was investigated. Peterson olefination of lactol (**39**), prepared by DIBAL reduction of butyrolactone[127], gave the ω-hydroxy ketene thioacetal (**40**) in 38% yield. Unfortunately, this compound isomerised to the dithioortholactone (**41**) which resisted all attempts at tosylation (Scheme 27). At this point it was realised that ketene thioacetals are less stable than azides, and should therefore be installed as late as possible in the synthetic sequence when preparing compounds like (**34**). This observation was fortuitous because the resulting synthesis of (**34**) proved easy, efficient and entirely reproducible for the large number of times that it was performed. Treatment of bromo ester (**36**) with sodium azide in DMF at room temperature gave azido ester (**43**) in high yield. Addition of this compound to 1 equivalent of BDP, followed by stirring at room temperature for 2 days, furnished the desired ω-azidoketene thioacetal (**34**) in 75% yield (Scheme 28). Lewis acids are known to decompose azides at room temperature[131] but the use of BDP did not present itself as a problem in the conversion of (**43**) to (**34**). The product (**34**) was readily purified by column chromatography, and was stable at room temperature, but slowly hydrolysed to the corresponding thioloester on storage unless water was rigorously excluded.

Part 2. Thermolysis of ω-Azido Ketene Thioacetal (**34**)

The intramolecular reaction proved more sluggish than its intermolecular counterparts and to overcome this, more forcing conditions were used by changing the reaction solvent from cyclohexane (b.p. 80-81°C) to *n*-octane (b.p. 128°C). In a typical experiment, a freshly prepared sample of (**34**) was dissolved in *n*-octane and heated at reflux (bath temperature 150°C) under an atmosphere of nitrogen. After 4 hours, starting material (**34**) was absent and TLC of the reaction mixture showed the presence of product (**38**) which had formed cleanly. Several attempts to isolate (**38**) were made but none of these was successful and removal of solvent led rapidly to the



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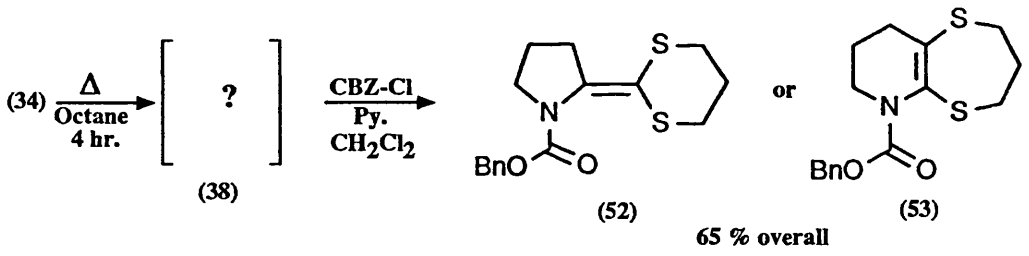

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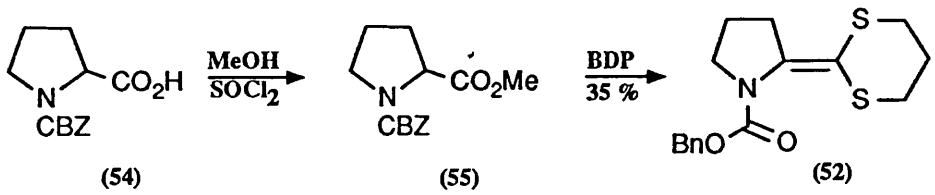
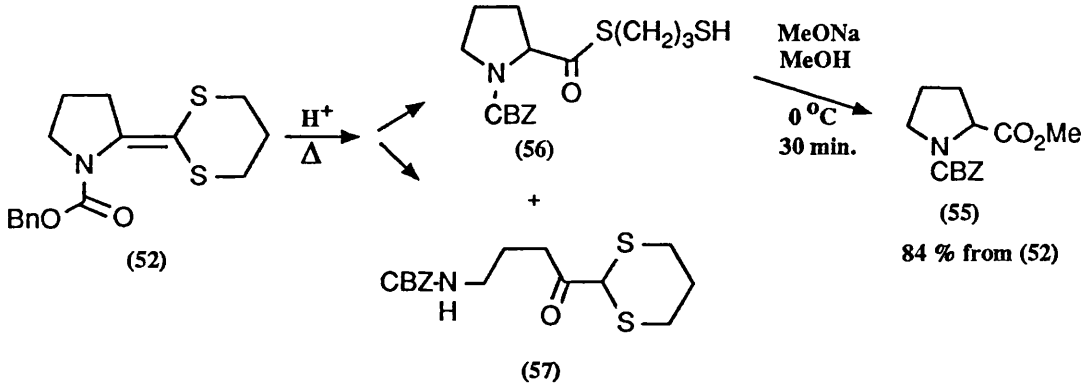


SCHEME 31.

formation of more polar products. At this point it is pertinent to discuss the various possible structures of (**38**). We presumed that azide (**34**) had undergone an intramolecular cycloaddition reaction[128] to give triazoline (**45**) which subsequently fragmented to the betaine (**46**) (Scheme 29). This betaine could then undergo hydride- or alkyl shift[129] to give (**47**) or (**48**) respectively. Alternatively, the betaine may rearrange to aziridine (**49**). Each of these transformations also involves loss of molecular nitrogen. In addition, either imine (**47**) or aziridine (**49**) could rearrange to the aminoketene thioacetal (**50**). Thus there were four possible structures for the thermolysis product (**38**), each having precedent in the literature[130]. Evidence which favours one of these structures over the other three is presented below.

Part 3. Trapping the Thermolysis Product (38)

Having failed to isolate (**38**), we attempted to produce a stable derivative by trapping the reactive species *in situ*. Since the four possible structures (**47**)-(**50**) each possess a nucleophilic nitrogen atom, we chose the electrophilic reagent, benzyl chloroformate (**51**). Following thermolysis of the azide (**34**) in *n*-octane, the resulting solution of (**38**) was cooled to 0°C, diluted with an equal volume of dichloromethane and then treated with benzyl chloroformate and pyridine. This led to a new compound which was isolated by column chromatography in 65% yield. The spectral data of the new compound were consistent with structure (**52**) (from intermediates (**47**), (**49**) or (**50**)) or with structure (**53**) (from intermediate (**48**)) (Scheme 20). Proof of structure was obtained by an independent synthesis of (**52**) starting from proline derivative (**54**). Esterification of (**54**) gave (**55**) which, when treated with BDP, led to the desired α-aminoketene thioacetal (**52**) in 35% yield (Scheme 31). Spectroscopic data of the compounds obtained by each route were identical. At this stage, we were able to eliminate structure (**48**) as the thermolysis product, leaving (**47**), (**49**) and (**50**) as possible structures for the unstable intermediate (**38**).



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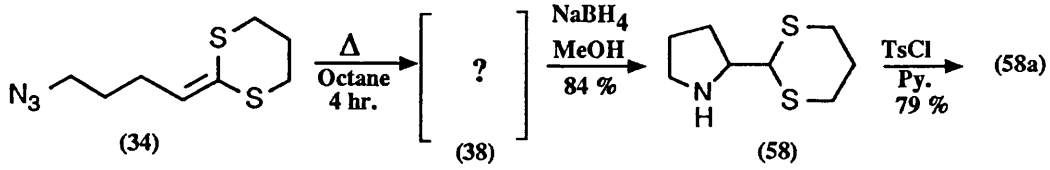


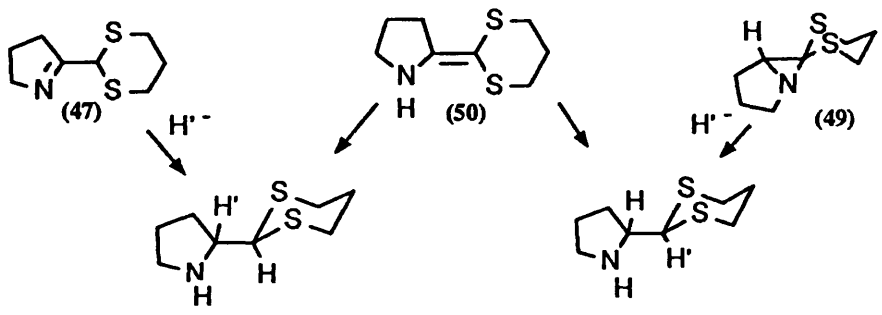
SCHEME 33.

Part 4. α-Amino Acids from α-Aminoketene Thioacetals

Ketene thioacetals are masked carboxylic acids.[103] This makes the α-aminoketene thioacetal (52) interesting since it is a masked form of the cyclic α-amino acid proline. Ketene thioacetals are readily hydrolysed by aqueous acid to give thioloesters[132], but the hydrolysis of α-aminoketene thioacetals to give α-amino acid derivatives has not previously been reported. The hydrolysis of α-aminoketene thioacetals is potentially complicated by the fact that they also contain an enamine functional group, which could hydrolyse to an amino ketone [133]. Refluxing a solution of (52) in 50% aqueous acetic acid led to a mixture of desired thioloester (56) (48%) and amino ketone (57) (8.2%) (Scheme 32). Alternatively, refluxing a solution of (52) in acetic acid which contained a small amount (2 drops per ml) of concentrated aqueous HCl gave only the desired product (56). This was converted to the methyl ester (55) in overall yield 84%. The transformation of (52) to (55) and of (55) to (52) demonstrates the synthetic equivalence of α-amino acids and α-aminoketene thioacetals. The synthesis of racemic proline derivative (55) was an important result for us because we had achieved our goal of preparing a cyclic amino acid using the intramolecular cycloaddition reaction outlined in the introduction. The various results obtained by exploiting this new reaction are set out in chapters 3, 4 and 5.

Part 5. Structure of the Thermolysis Product (38)

Two experiments helped to shed light on the structure of the thermolysis product (38), one of which was carefully designed while the other was somewhat fortuitous. The first experiment was based on the observation that compound (38) could be reduced *in situ* to give pyrrolidine (58). Following thermolysis of a solution of (34), the reaction mixture was cooled to 0°C then treated with methanol and sodium borohydride. After 30 minutes, the reduced product (58) was obtained in 84%



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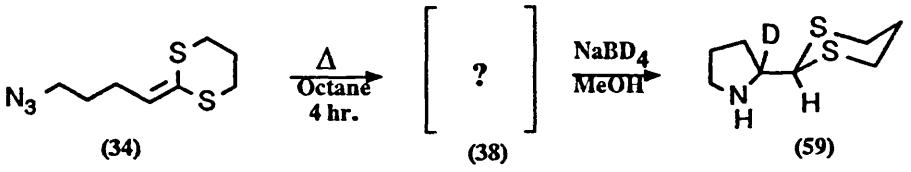

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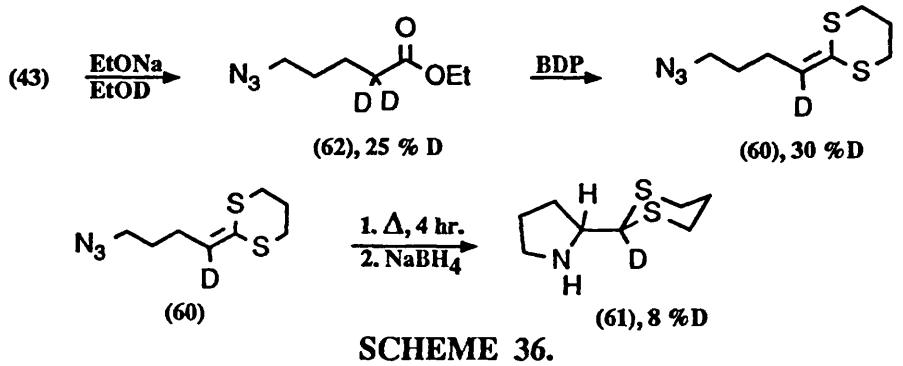

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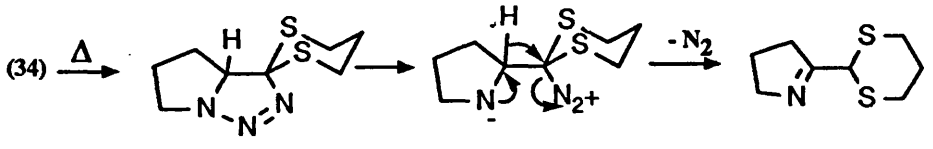
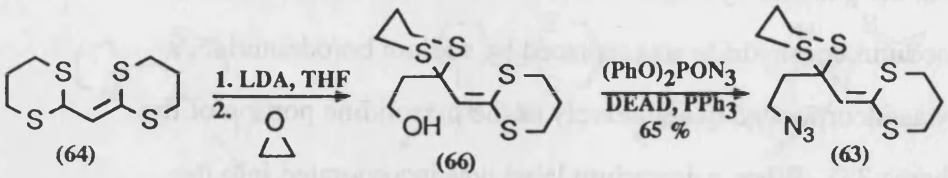


SCHEME 37.

yield (Scheme 33). This result is interesting because the hydride ion can be delivered to one of two carbon atoms, depending on the structure of (**38**) (Scheme 34). Use of deuterium labels in the place of hydrogen should reveal which carbon atom is reduced. When sodium borohydride was replaced by sodium borodeuteride, a deuterium atom was incorporated quantitatively in the pyrrolidine portion of the product (**59**) (Scheme 35). When a deuterium label was incorporated into the cyclisation precursor (**60**), and the reduction of the thermolysis product was carried out with sodium borohydride, deuterium was present in the dithiane portion of the product (**61**) (Scheme 36). The labelled ketene thioacetal (**60**) was prepared from (**43**) as follows; a solution of (**43**) in D-ethanol (C_2H_5OD) was treated with a catalytic amount of sodium ethoxide which, after 12 hours, gave deuterated azido ester (**62**) containing 25% deuterium at C-2. Treatment of (**62**) with BDP then gave ketene thioacetal (**60**) with 30% deuterium at C-2. The slight increase in the proportion of deuterium which accompanied the conversion of (**62**) to (**60**) probably reflects a kinetic isotope effect

This labelling experiment shows that the cyclisation product (**38**) cannot be the aziridine (**49**), since this would be expected to give the reverse labelling pattern. This leaves either cyclic imine (**47**) or α-aminoketene thioacetal (**50**) as possible structures for the thermolysis product (**38**). However, reduction of deuterium-labelled (**50**) using methanolic sodium borohydride should result in complete loss of deuterium into the solvent. Since this was not observed, it is reasonable to assume that the structure of cyclisation product (**38**) is the cyclic imine (**47**). A possible mechanism for the formation of (**38**) is set out in Scheme 37. The fact that a proportion of the deuterium label was lost during the thermolysis/reduction process may reflect slow isomerization of (**47**) to (**50**) under the reduction conditions. Alternatively, there may be a kinetic isotope effect for the cyclization reaction, but we did not investigate this aspect any further.



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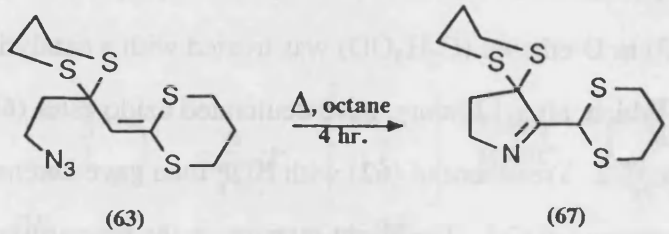

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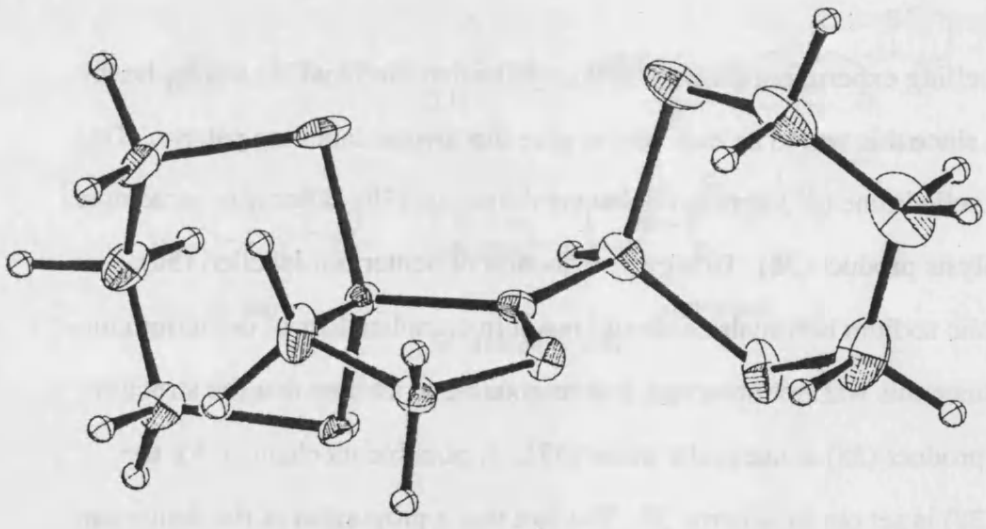
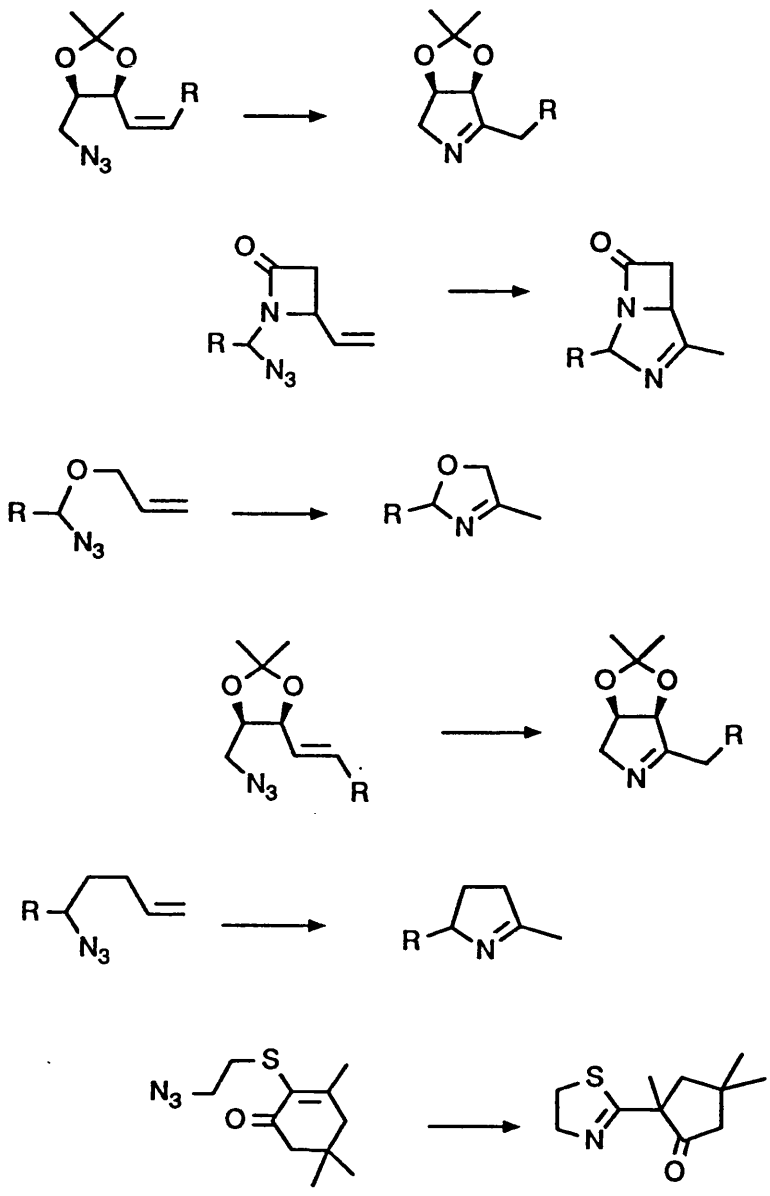


Figure 2., ORTEP drawing of (67)

The second experiment, which quite unexpectedly gave support for the formation of the cyclic imine (**47**), involved cyclisation of the more highly functionalized ω-azidoketene thioacetal (**63**). This compound was prepared by deprotonation of the known ketene thioacetal (**64**)[134] to give the symmetrical allylic anion (**65**). Alkylation with ethylene oxide gave alcohol (**66**) which was converted to (**63**) using diphenylphosphoryl azide[135] (Scheme 38). Thermolysis of azide (**63**) in *n*-octane for 4 hours led cleanly to a new product. We were surprised to find that this new product was unreactive towards both benzyl chloroformate and sodium borohydride. Indeed the cyclisation product of this reaction was anything but unstable and could be isolated by column chromatography. Recrystallization gave crystals suitable for X-ray analysis and the product was shown to be the cyclic imine (**67**)[211] (Scheme 39). The ORTEP drawing of (**67**) is shown in Figure 2.

The formation of cyclic imine (**67**) from (**63**) does not, of course, prove that thermolysis of (**34**) also leads to a cyclic imine. It does, however, provide circumstantial evidence which supports this theory as do the other results described above. For this reason, we have used imine (**47**) as the structure of thermolysis product (**38**). There are numerous precedents from the literature of azido alkenes which give cyclic imines on thermolysis, some of which are set out in Scheme 40[136]. These examples include an important early contribution from Logothetis in 1965.



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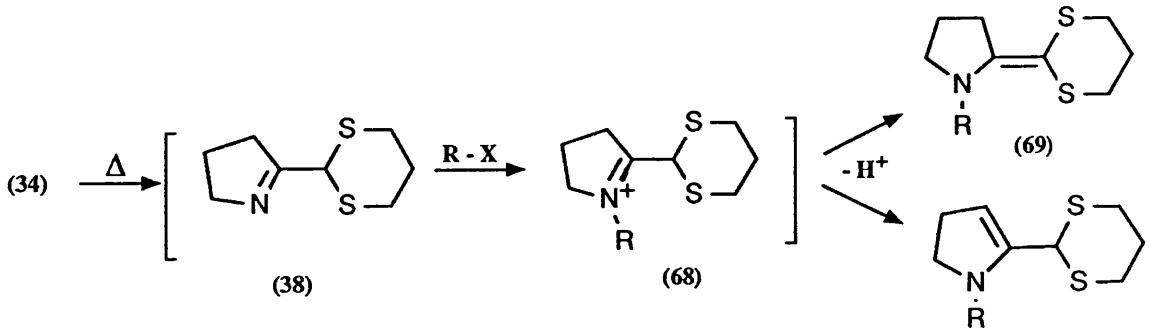
CHAPTER 3



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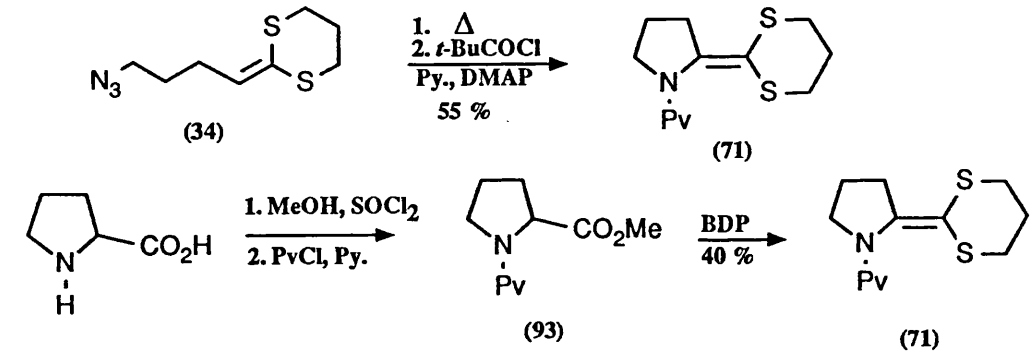

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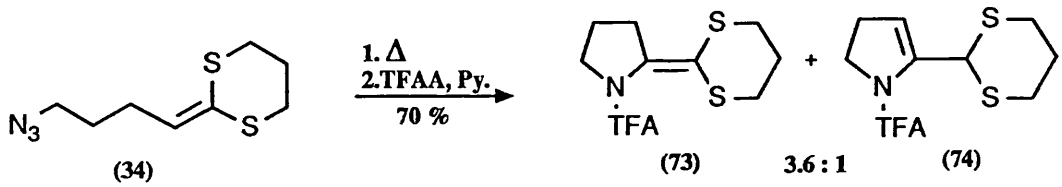

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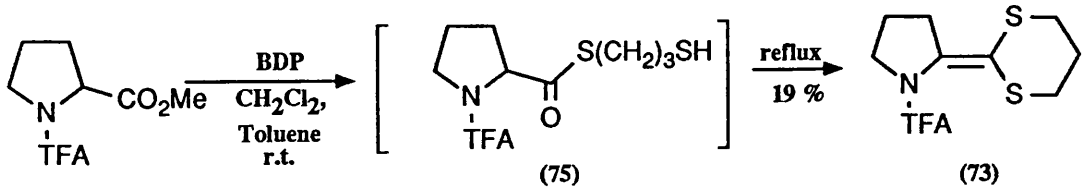


SCHEME 44.

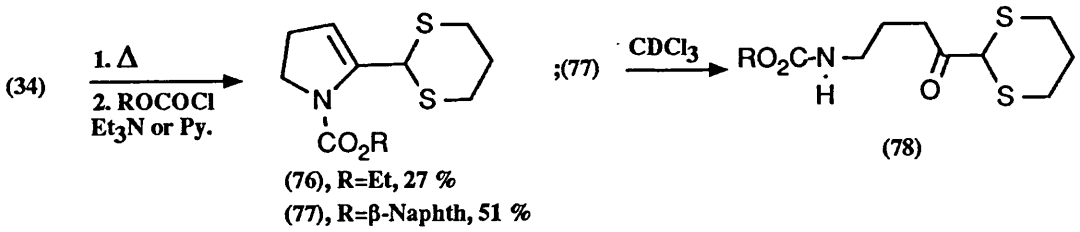
CHAPTER 3

The Scope of the Intramolecular Azide Cycloaddition Reaction

Part 1. Trapping the Imine (38) with Various Electrophiles

The imine (**38**), produced by thermolysis of ω-azidoketene thioacetal (**34**), can react with an electrophile to give two products (**69**) or (**70**), assuming that an intermediate of structure (**68**) is involved. (Scheme 41) The previous chapter described the reaction of (**38**) with benzyl chloroformate to give (**69**, R = CO_2Bn) in 65% yield. By analogy, when (**38**) was treated with pivaloyl chloride and pyridine at 0°C, then allowed to warm to room temperature, the α-aminoketene thioacetal (**71**) was produced in 55% yield. Identical material was prepared from proline derivative (**93**)[225],using methodology established in Chapter 2 (Scheme 42). The imine (**38**) also reacted with trifluoroacetic anhydride to give a mixture of the two tautomers (**73**) and (**74**) in a ratio of 3.6:1 (as judged by ^1H NMR) and in 70% yield (Scheme 43). A pure sample of (**73**) was prepared from the appropriate proline derivative by treatment with BDP, first at room temperature then at reflux. This transformation proceeded via thioloester (**75**), which could be isolated (Scheme 44). The absence of tautomer (**74**) from the product of this reaction presumably reflects the fact that different intermediates are involved in the two pathways.

In contrast to the reactions described above, which gave exclusively or mostly the tautomer (**69**), reaction of imine (**38**) with either ethyl chloroformate or β-naphthyl chloroformate[137] gave tautomer (**70**). Reaction with ethyl chloroformate gave adduct (**76**) (27% yield) while β-naphthyl chloroformate gave (**77**) (51% yield) (Scheme 45). Enamine (**77**) was prepared with the hope that an X-ray analysis would be possible, but suitable crystals could not be obtained. The enamine portion of (**77**) was hydrolysed on standing for several hours in deuterochloroform, to give the amino



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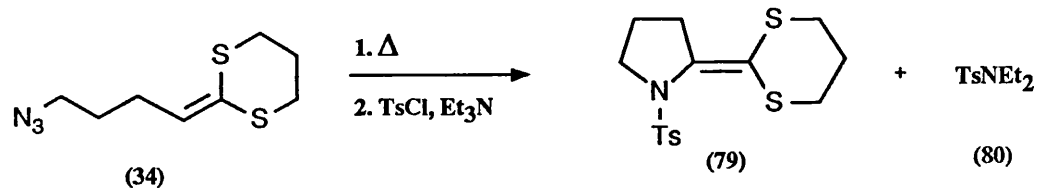

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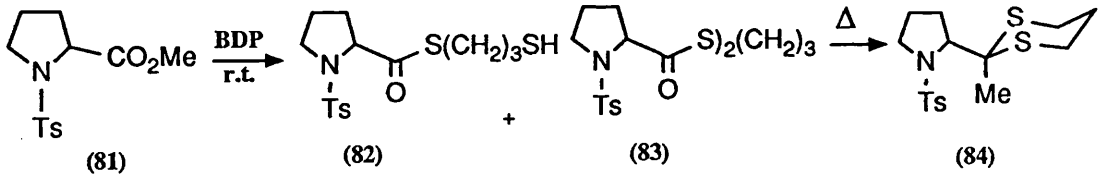

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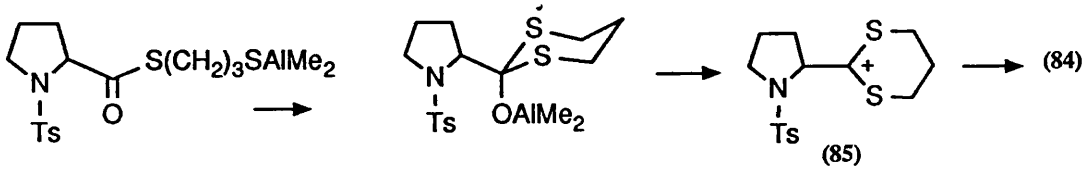


SCHEME 48.

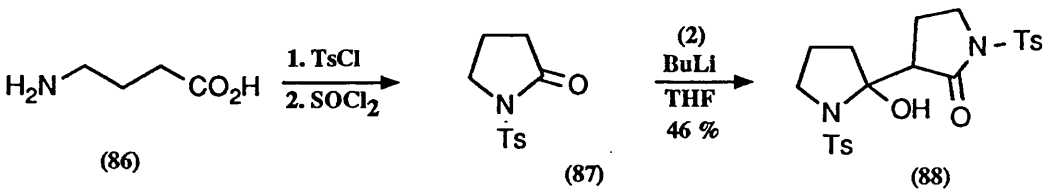
ketone (**78**). The ^1H NMR spectra of compounds (**76**) and (**77**) contain a characteristic triplet due to the vinyl proton in addition to an unusually broad, low-field singlet due to the dithiane C-2 proton. The appearance and position of the latter peak may reflect the presence of a weak intramolecular hydrogen bond to the carbamate oxygen.[213]

In addition to the electrophilic reagents described above, various other reagents were tried in an attempt to derivatize (**38**) but these met with less success. Addition of tosyl chloride and triethylamine to (**38**) gave an adduct whose NMR and mass spectra are consistent with structure (**79**) (Scheme 46). Unfortunately, (**79**) could not be separated from the byproduct (**80**) which resulted from attack of tosyl chloride by triethylamine, and so the adduct (**79**) could not be fully characterised. Use of pyridine or DBU in place of triethylamine gave none of the desired product. Two alternative attempts to prepare a sample of (**79**) were also unsuccessful. Treatment of proline derivative (**81**) with BDP gave the two thioloesters (**82**) and (**83**). Heating the reaction mixture led additionally to dithiane (**84**) (Scheme 47). Product (**84**) presumably arises from attack of the dithiolium cation (**85**) by some methyl aluminium species present in the reaction mixture (Scheme 48). The second approach to (**79**) involved an attempted Peterson olefination of the 2-pyrrolidinone (**87**) prepared from γ-amino butyric acid (**86**)[138] (Scheme 49) . Unfortunately, treatment of 2-lithio-2-trimethylsily-1,3-dithiane with (**87**) gave aldol adduct (**88**) in 46% yield but none of the desired ketene thioacetal (**79**).

Finally, treatment of cyclic imine (**38**) with the reagents di-*tert*-butyldicarbonate (BOC-anhydride) and trifluoromethanesulphonic anhydride (triflic anhydride) gave only complex mixtures of products.

Part 2. The Hydrolysis of Cyclic α-Aminoketene Thioacetals

The hydrolysis of the cyclic α-aminoketene thioacetal (**52**) to give (**56**) and



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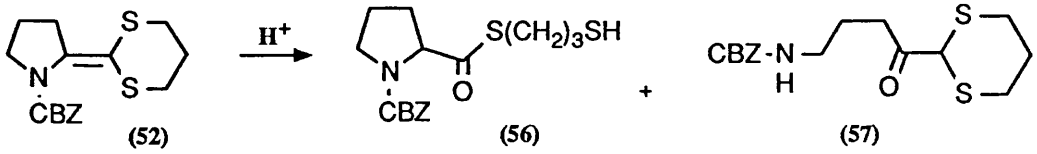

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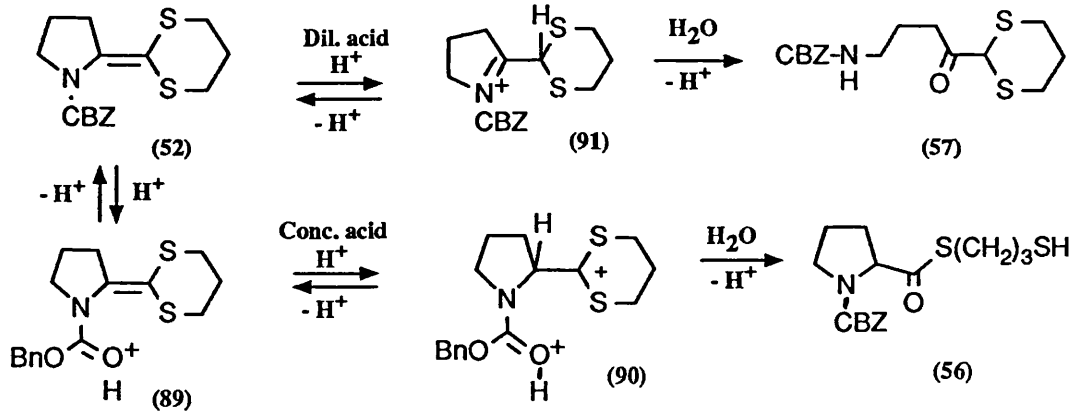

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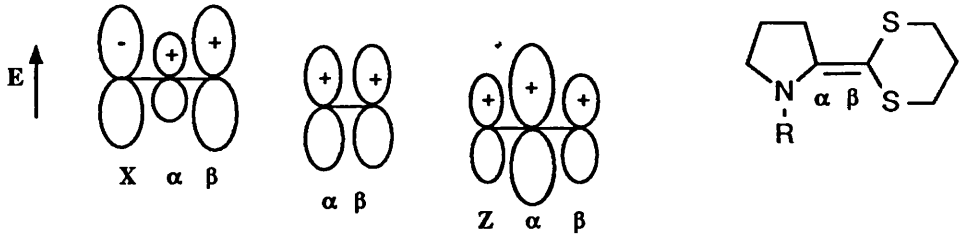
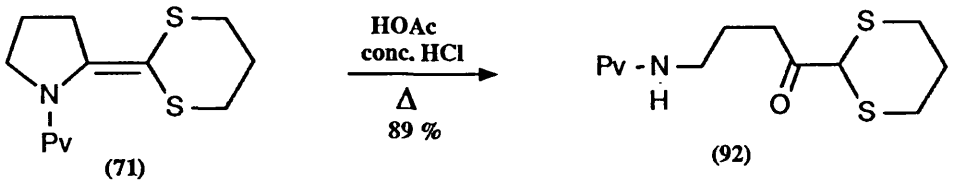


Perturbation of ethylene HOMO
X = π -donating
Z = π-withdrawing

Figure 3.

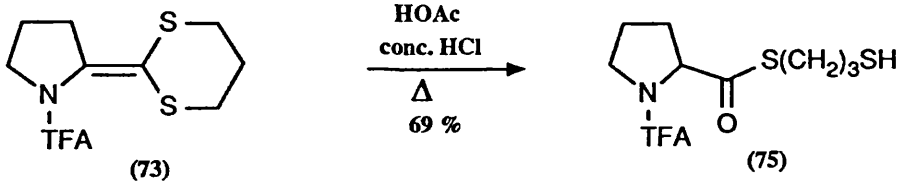
(57) was described in the previous chapter. Strongly acidic conditions led exclusively to the desired thioloester (56) whereas the use of more dilute acid gave a mixture of (56) and the amino ketone (57) (Scheme 50). One explanation of these results is that, under strongly acidic conditions, the ketene thioacetal (52) is protonated initially on the carbonyl oxygen to give (89) and then additionally at the alkene. The diprotonated intermediate (90) is then trapped by water to give thioloester (56). When dilute acid is used, the chance of forming the diprotonated species (90) is small and so hydrolysis occurs *via* the monoprotonated intermediate (91) (Scheme 51). The regioselectivity of protonation can be explained in terms of perturbational molecular orbital theory,[139] assuming that in both protonated and unprotonated species [(89) and (52)] the nitrogen substituent has the dominant perturbational effect on the HOMO of the alkene. Figure 3 shows the way in which the HOMO energy level and coefficients of ethylene change when electron-donating and electron-withdrawing groups are introduced. In unprotonated species (52), the nitrogen is π-donating which increases the C-β HOMO coefficient and causes protonation to occur faster at C-β. The protonated species (89) has an electron-withdrawing substituent at nitrogen which increases the C-α HOMO coefficient and causes protonation to occur faster at C-α. This application of perturbational molecular orbital theory is rather crude since it ignores the influence of sulphur, but it nevertheless accounts for the observed products in this example and others (*vide infra*). A frontier orbital treatment also ignores the presence of charge-charge interactions which may be important in alkene protonation, but there is a reasonable correlation between HOMO coefficients and charge distribution in simple systems.

The N-pivaloyl ketene thioacetal (71) provided a good testing ground for the theory outlined above. As will be discussed below, it was important that we should be able to effect hydrolysis of (71) to give the thioloester (72), thus exposing the masked α-amino acid functionality present in (71). Our initial attempts at this transformation were in vain since heating (71) in a mixture of acetic acid and concentrated HCl at



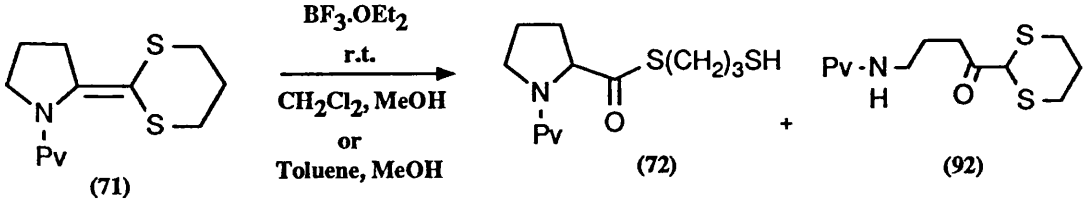
(71) (92)

SCHEME 52.



(73) (75)

SCHEME 53.



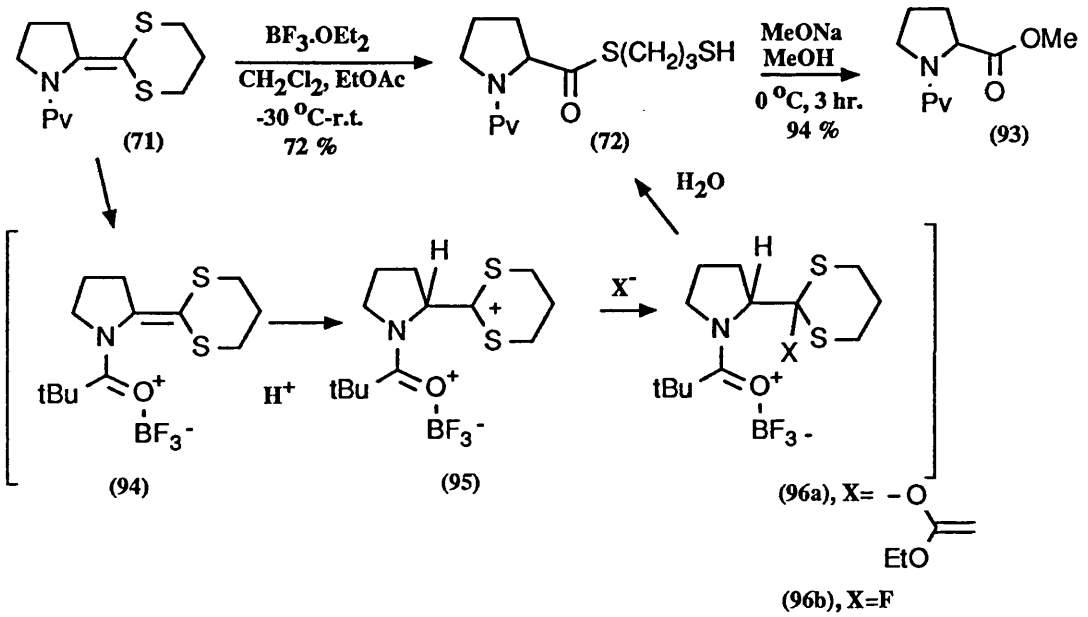
(71) (72) (92)

SCHEME 54.

reflux gave the undesired amino ketone (**92**) in 89% yield (Scheme 52). Various other protic conditions were examined but none gave the desired thioloester (**72**). Apparently the pivalamide group with its electron-releasing *tert*-butyl moiety forces protonation to occur at C-β, even under strongly acidic conditions. Alternatively, the steric bulk of the *tert*-butyl group may force the amide group to be non-planar, giving the alkene more enamine character.

Two solutions to the problem of regioselectivity in the hydrolysis of (**71**) were designed and tested. The first solution was to replace the three electron-releasing methyl groups of the pivalamide by electron-withdrawing fluorine atoms, i.e. to use the trifluoroacetamide protecting group on nitrogen. Exposure of α-aminoketene thioacetal (**73**) to the normal acid hydrolysis conditions led exclusively to the thioloester (**75**), which was isolated in 69% yield (Scheme 53). Thioloester (**75**) prepared in this way was identical to material prepared directly from proline as described earlier. Unfortunately the trifluoroacetamide group is very labile under basic conditions[140] and so use of this protecting group was not an ideal solution in a general synthetic sense (*vide infra*).

The second potential solution was to return to the pivalamide compound (**71**) but to change the hydrolysis conditions. Inspired by a report by Corey[141] that alkenes will undergo addition reactions when treated with boron trifluoride, the effect of this Lewis acid on the hydrolysis of (**71**) was investigated. Initially, the substrate was dissolved in toluene or dichloromethane which contained a small amount of methanol, then treated with boron trifluoride etherate. This led to mixtures of thioloester (**72**) and amino ketone (**92**) (Scheme 54). The reaction could be more carefully controlled by cooling a solution of (**71**) to -30°C under nitrogen before adding the Lewis acid, and by replacing methanol with ethyl acetate (Scheme 55). This led cleanly to the desired hydrolysis product (**72**) in 72% yield. Thioloester (**72**) was converted to the methyl ester (**93**) using a solution of sodium methoxide in methanol. A possible mechanism



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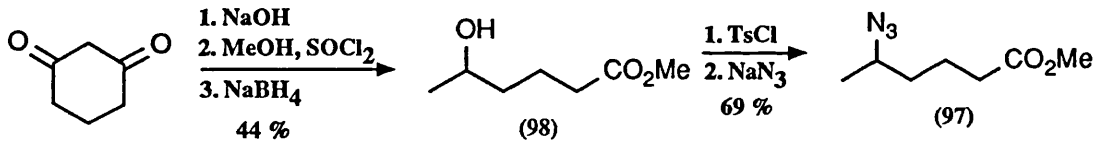

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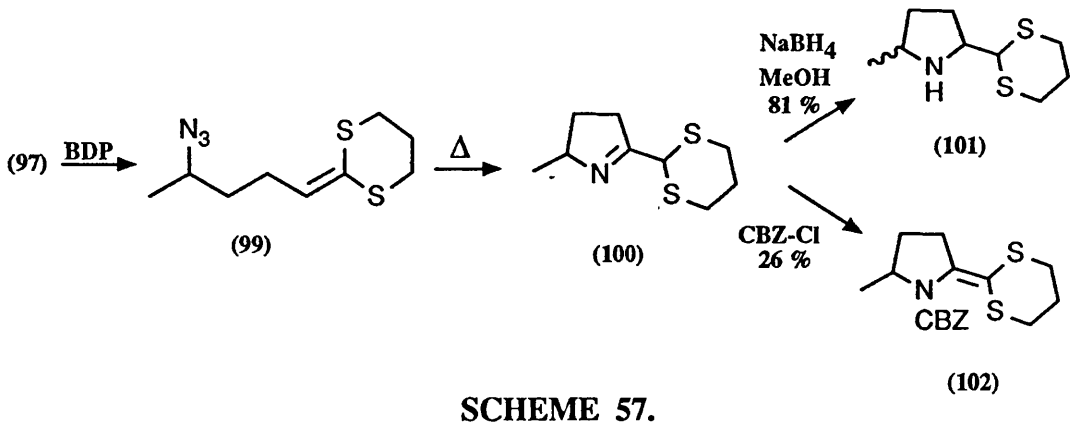


SCHEME 57.

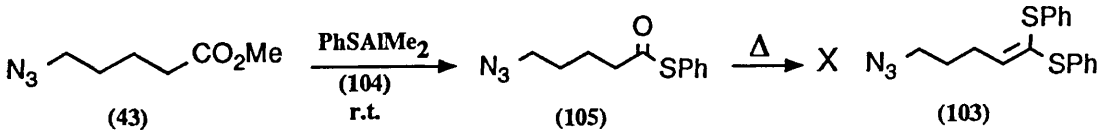
for this process is set out in Scheme 55. The amide oxygen of (**72**) could form a complex with the Lewis acid to give (**94**). Protonation of (**94**) would lead to (**95**) which could be trapped by ethyl acetate to give dithioorthoester (**96a**), or by fluoride to give (**96b**). Either intermediate would be hydrolysed on aqueous work-up to give the observed thioloester (**72**). Thus, complexation of the pivalamide group by a Lewis acid has a similar effect to replacing it with a trifluoroacetamide group. The boron trifluoride mediated hydrolysis was also applicable to a number of derivatives of (**72**) (*vide infra*). Variation of the conditions, to provide other sources of proton and nucleophile, was not explored.

In summary, we believe that the presence of a strongly electron-withdrawing substituent on the nitrogen atom of an aminoketene thioacetal, be it a trifluoroacetamide group, a protonated carbamate or a Lewis acid-complexed pivalamide, favours protonation of the alkene at the carbon atom adjacent to nitrogen. Other conditions lead to protonation of the alkene partly, or entirely, at the alternative position.

Part 3. Thermolysis of some different cyclisation precursors

To investigate the scope of the intramolecular 1,3-dipolarcycloaddition reaction introduced in chapter 2, various other ω-azidoketene thioacetals were prepared. The secondary azide (**97**) was prepared from cyclohexane-1,3-dione[142] in five steps via hydroxy ester (**98**) (Scheme 56). Treatment of (**97**) with BDP gave ketene thioacetal (**99**) in 66% yield and this compound was transformed cleanly on heating in refluxing octane to give (**100**), presumed to be the cyclic imine (Scheme 57). Imine (**100**) was not isolated, but could be reduced efficiently using sodium borohydride in methanol to give the 2,5-disubstituted pyrrolidine (**101**) as a 1:1 mixture of diastereomers. In addition, the imine (**100**) reacted with benzyl chloroformate to give the α-aminoketene thioacetal (**102**), but the yield of this reaction was only 26%.

Out next approach was to modify the ketene thioacetal portion of the



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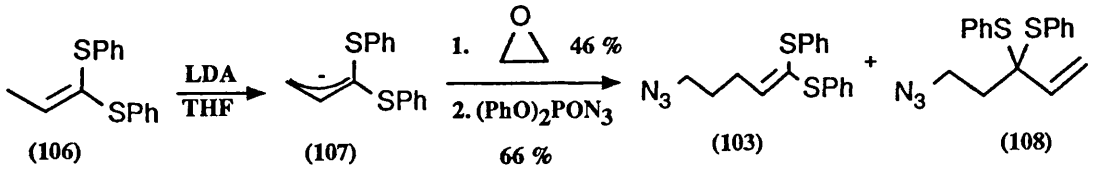

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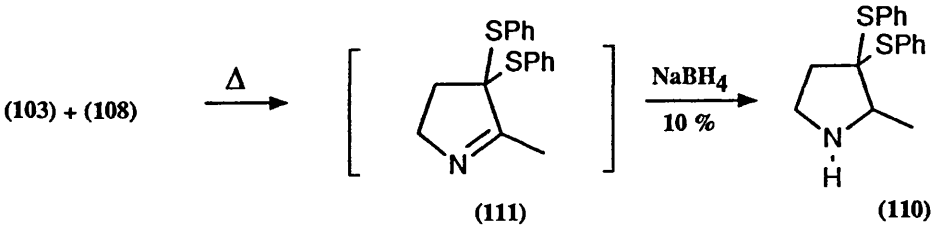

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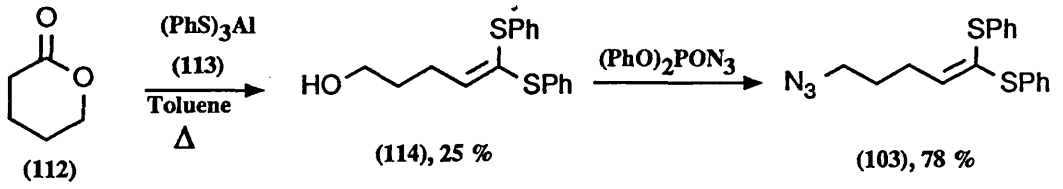


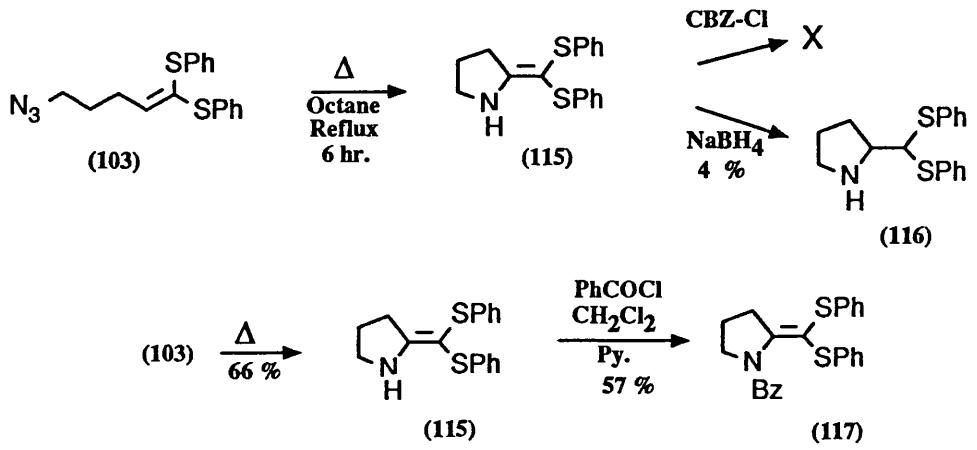
SCHEME 61.

cyclisation precursor. All the ketene thioacetals described above have the two sulphur atoms joined by a trimethylene bridge i.e. they are derivatives of 1,3-dithiane. This group was chosen because of its ease of preparation and because the alkene portion of the ketene thioacetal is relatively unhindered. We wondered whether the S,S′-diphenyl ketene thioacetal (**103**) would undergo intramolecular cycloaddition or whether the alkene would be too hindered, since earlier studies on a related compound suggested that each face of the alkene was blocked by a phenyl group[143].

The synthesis of (**103**) was not as straightforward as that of the dithianyl derivative (**34**) because the preparation of S,S′- diphenyl ketene thioacetals requires more forcing conditions. Treatment of azido ester (**43**) with the preformed trimethylaluminium/thiophenol reagent (**104**) gave only the thioloester (**105**) at room temperature while use of elevated temperatures led to decomposition (Scheme 58). An alternative approach was the alkylation of allylic anion (**107**) derived from ketene thioacetal (**106**)[144]. The crude adduct of (**107**) and ethylene oxide was then converted to the mixture of desired azide (**103**) and isomeric compound (**108**), which could not be separated (Scheme 59). The mixture of products resulted from the fact that alkylation of anion (**107**) was not regioselective, and occurred at both the α- and the γ- positions in an approximate ratio of (1:1). This lack of selectivity is surprising since anion (**107**) is known to react predominantly at the γ-position with other electrophiles.[143]

Thermolysis of the mixture of azides led to a new product. After an hour in refluxing *n*-octane, one azide was absent from the reaction mixture as judged by (TLC) while the other remained. The crude reaction mixture was treated with sodium borohydride and the product was isolated. This product was found to be pyrrolidine (**110**), presumably formed by reduction of imine (**111**), showing that the undesired azide had cyclized leaving the other azide mostly or entirely unreacted (Scheme 60).

To avoid the complication of inseparable impurities, we required a route



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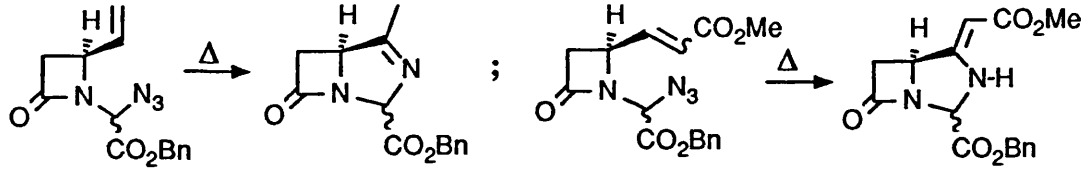

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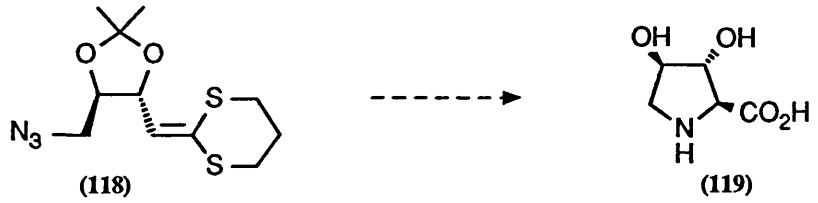

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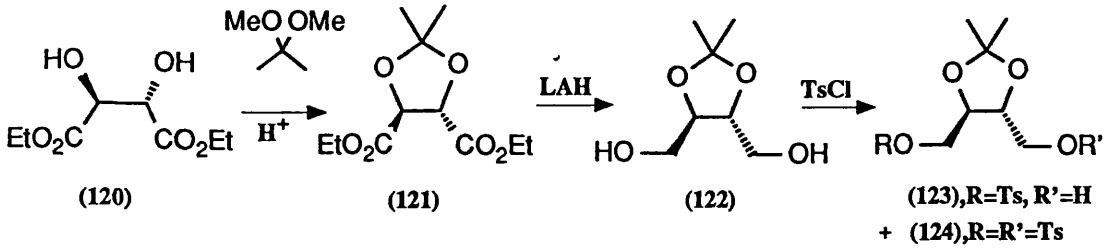
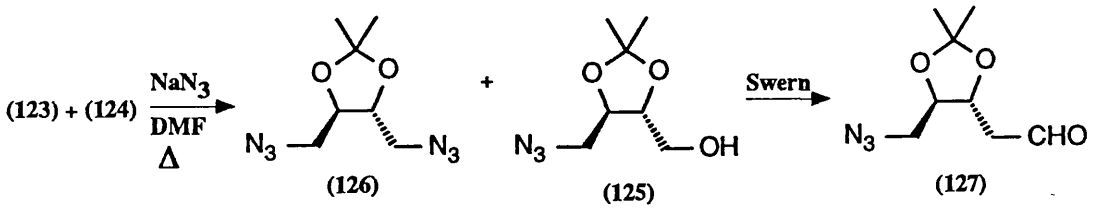


SCHEME 65.

which would lead to pure azide (**103**). This was eventually achieved starting from δ-valerolactone (**112**) which, when treated with aluminium tris (phenylthiolate) (**113**)[144] and heated under reflux, led to the hydroxy ketene thioacetal (**114**) in 25% yield (Scheme 61). The alcohol function was then converted directly to the corresponding azide, giving (**103**) in 78% yield. With a pure sample of this azide in hand, we were able to try a thermolysis experiment. Heating a solution of (**103**) in octane for six hours led cleanly to the α-aminoketene thioacetal (**115**). Based on the assumption that the cyclisation product was unstable, we initially tried to trap it *in situ*. However, no reaction occurred with benzyl chloroformate while prolonged reaction with sodium borohydride gave only a very low yield of the corresponding pyrrolidine (**116**) (Scheme 62). We then discovered that the cyclisation product (**115**) was not unstable as originally thought, but could be purified by chromatography and was isolated in 66% yield. We also found that (**115**) reacted with benzoyl chloride to give amide (**117**) in 57%. This acylation could also be performed using the crude thermolysis product, and the overall yield of (**117**) from (**103**) was then 52% (Scheme 62).

It is interesting to note that the cyclisation product (**115**) exists as the enamine tautomer rather than the cyclic imine. This may be due to the enhanced acidity of the bis (phenylthio) methine proton (pK_A of bis (phenylthio)methane = 30.8) compared to the corresponding proton in cyclic imine (**38**) (pK_A of 1,3-dithiane = 39)[109]. Alternatively, this tautomer may be stabilised by π-delocalisation through the sulphur substituents. In a related example from the literature, changing the alkenyl substituent from hydrogen to methoxycarbonyl switched the product from a cyclic imine to an exocyclic enamine[130b] (Scheme 63).

Another ω-azido ketene thioacetal which helped to test the scope of the reaction is compound (**118**), which was designed as a precursor to the cyclic amino acid (2S, 3R, 4R)-3,4-dihydroxyproline (**119**)[145] (Scheme 64). We wanted to demonstrate



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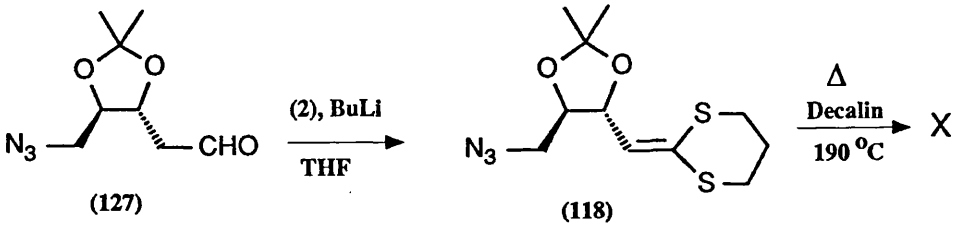

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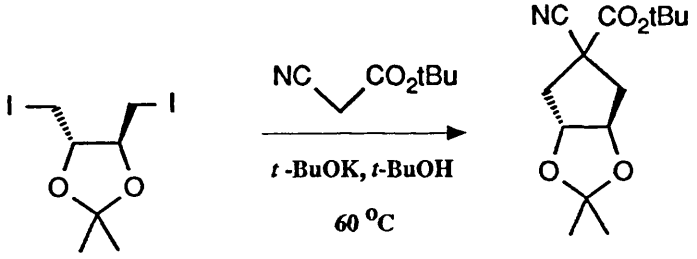

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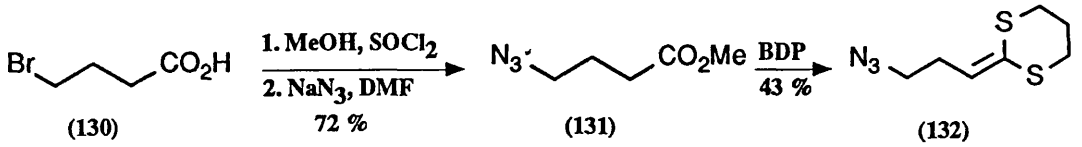
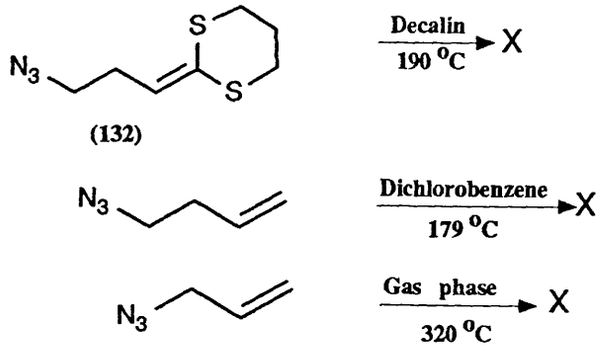


SCHEME 69.

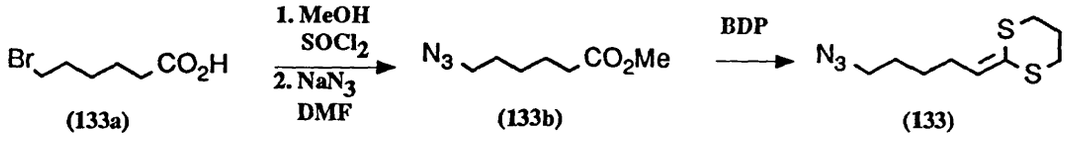
an application of the cyclization reaction by preparing a substituted azide as the precursor to the corresponding substituted proline derivative, as will be discussed in more detail in the next chapter. Azide (**118**) was prepared in six steps from (-)-diethyltartrate (**120**). Protection of the diol function of (**120**) gave the acetonide (**121**)[146] which was reduced using lithium aluminium hydride (LAH) to give the diol (**122**)[147]. Treatment of (**122**) with one equivalent of tosyl chloride led to a mixture of desired monotosylate (**123**) along with the ditosylate (**124**) and recovered starting material[148] (Scheme 65). Treatment of the mixture of tosylates (**123**) and (**124**) with sodium azide in DMF gave the known azide (**125**)[222,223] and easily removed diazide (**126**). The yield of (**125**) from diol (**122**) was 34% (Scheme 66). Oxidation of the alcohol (**125**) using the method of Swern[149] gave 77% of aldehyde (**127**). Peterson olefination of (**127**) using the anion of (**2**) gave the desired ketene thioacetal (**118**) in 10% yield. The yield of this step was low, possibly because aldehyde (**127**) was thought to exist partially in the hydrated form. No attempt was made to improve the yield of this step because unfortunately the ketene thioacetal (**118**) did not undergo intramolecular cyclisation, even at elevated temperatures (Scheme 67). This failure to give the *trans*-fused [3.3.0] bicyclooctane clearly represents a limitation of the cyclisation reaction, but was not entirely unexpected because the activation energy needed to produce the highly strained bicyclic product is presumably too high for the reaction to take place, even at 190°C. It is, however, interesting to note that double alkylation of the diiodo compound (**128**) to give the *trans*-fused bicyclic product (**129**) took place efficiently at 60°C[150] (Scheme 68).

Part 4. Approaches to larger and smaller rings

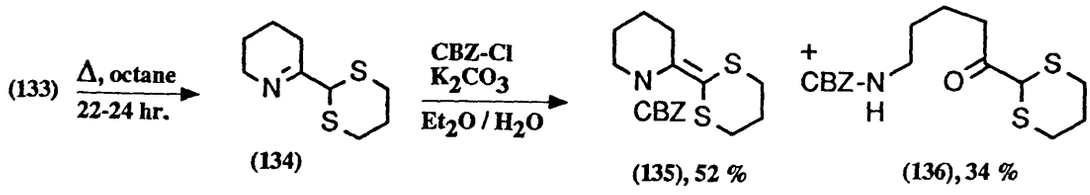
The precursor to the four-membered ring was prepared by analogy with the five-membered ring precursor (**34**). 4-Bromobutanoic acid (**130**) was esterified then treated with sodium azide to give azido ester (**131**) in 72% yield (Scheme 69). Conversion of the ester to the desired ketene thioacetal (**132**) proceeded in 43% yield.



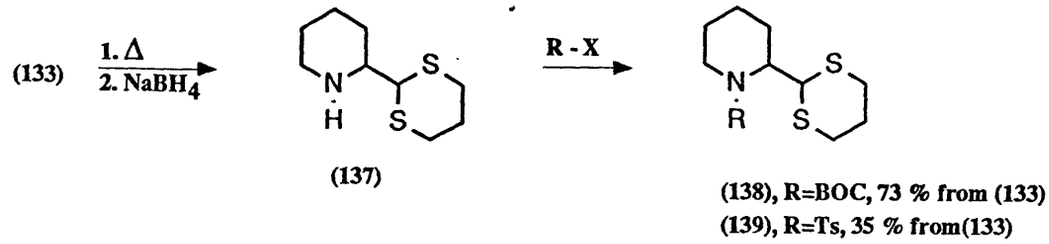
SCHEME 70.



SCHEME 71.



SCHEME 72.

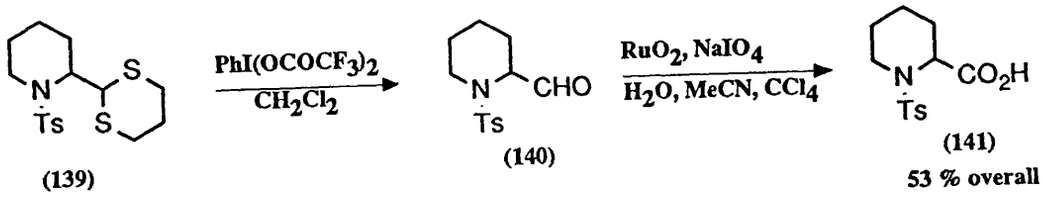


SCHEME 73.

Thermolysis of (**132**) in *n*-octane at 150°C gave no new products, while increasing the temperature to 190°C with decalin as solvent also gave no reaction, and the substrate could be recovered unchanged. We were disappointed that the cyclisation reaction could not be used to construct four-membered rings but comforted by a related report that homoallyl azide does not cyclise in 1,2-dichlorobenzene at 179°C while allyl azide is recovered unchanged after being heated to 320°C in the gas phase[130a] (Scheme 70).

Fortunately, our attempts at the construction of six-membered rings met with more success. The desired cyclisation precursor (**133**) was constructed from 6-bromohexanoic acid by analogy with compounds (**34**) and (**132**) (Scheme 71). Compound (**133**) was dissolved in *n*-octane and heated under reflux for 24 hours, which led cleanly to a new product presumed to be cyclic imine (**134**). This compound could not be isolated and reacted only slowly with benzyl chloroformate; indeed benzyl chloroformate was decomposed by pyridine faster than it reacted with (**134**). Use of a two-phase system with aqueous potassium carbonate as base was more successful, and gave the α-aminoketene thioacetal (**135**) in 52% yield (Scheme 72). In addition, the amino ketone (**136**), presumed to arise from hydrolysis of (**134**) followed by acylation, or directly from (**135**), was isolated in 34% yield.

Since the α-aminoketene thioacetal (**135**) is a masked version of the cyclic α-amino acid pipecolic acid, we hoped to be able to hydrolyse the ketene thioacetal portion of (**135**) selectively, and thus to prepare the cyclic α-amino acid. Unfortunately the various conditions which we used for hydrolysis all gave the undesired amino ketone (**136**). A less direct route to pipecolic acid was eventually taken, involving reduction of cyclic imine (**134**). Following thermolysis of azide (**133**), the cyclic imine (**134**) was treated with methanol and sodium borohydride to give the piperidine (**137**), which was protected as the BOC derivative (**138**) (Scheme 73). The overall yield for this process was 73%, demonstrating the efficiency of the cyclisation step, but attempts to deprotect the dithiane group were unsuccessful due to the instability of the resulting



(139) (140) (141)

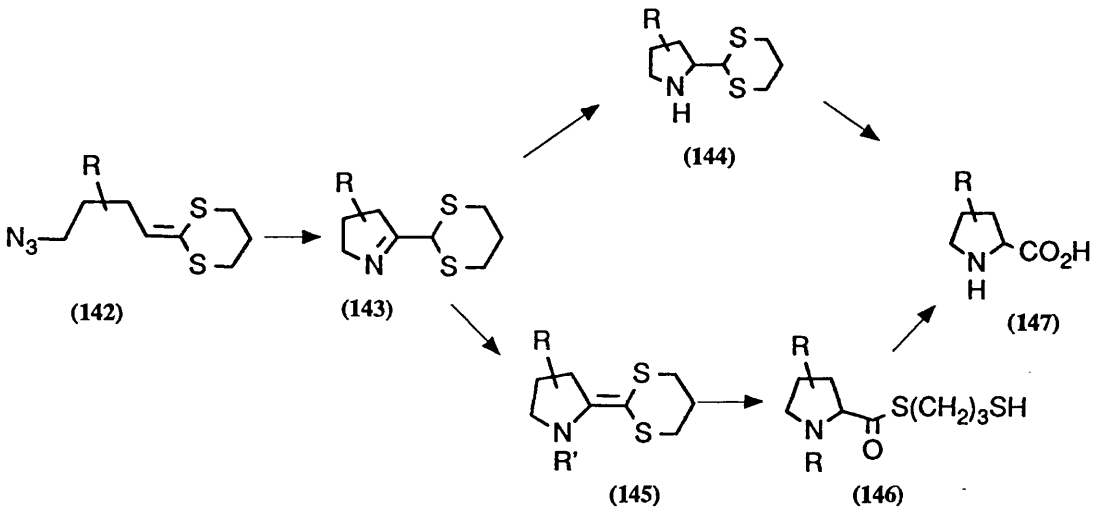
53 % overall

SCHEME 74.

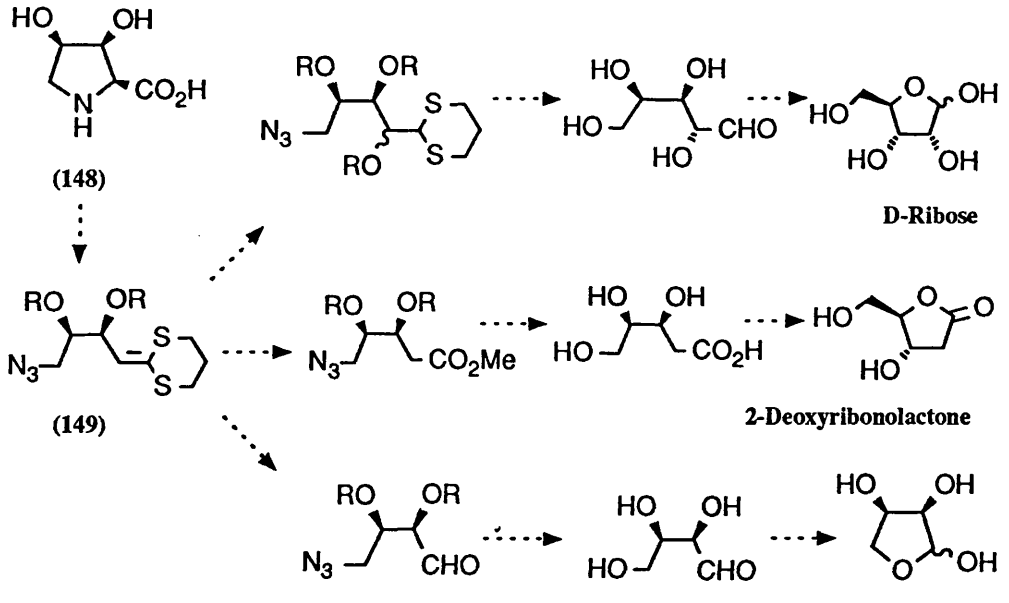
aldehyde. This problem was overcome by changing the amine protecting group from BOC to tosylate. Tosylation of the crude reduction product was not successful and so the piperidine (**137**) was isolated (58% yield) and then treated with tosyl chloride and pyridine to give the N-tosylate (**139**) in 61% yield. Deprotection of the dithiane group was best achieved with bis (trifluoroacetoxy)iodobenzene, a reagent introduced recently by Stork[151]. The resulting aldehyde (**140**), which has been reported previously[219], was then oxidised using sodium periodate and catalytic ruthenium dioxide, in which the reactive species is thought to be ruthenium tetroxide[152]. The yield of carboxylic acid (**141**) was 53% from the dithiane (**139**) (Scheme 74). The spectral data of compound (**141**) were identical to those of an authentic sample prepared by tosylation[138a] of commercially available pipecolic acid. In addition, the spectral data of the dicyclohexylamine salt of (**141**) agreed with the literature values[153]. Thus, thermolysis of azide (**133**) was shown to be a viable route to the corresponding cyclic α-amino acid.

In summary we have shown that cyclization of ω-azidoketene thioacetals can be used to construct pyrrolidine rings and that this reaction can tolerate a variety of changes in both the cyclization precursor and in the conditions used to trap the cyclization product. The methodology was successfully extended to the preparation of piperidine derivatives but could not be used to construct the four-membered azetidine ring.

CHAPTER 4



SCHEME 75



SCHEME 76.

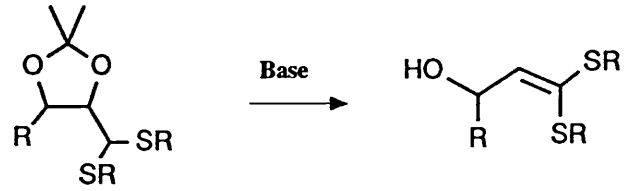
CHAPTER 4

A Synthesis of (2S, 3S, 4R)-3,4-Dihydroxyproline based on the Intramolecular Azide Cycloaddition Reaction.

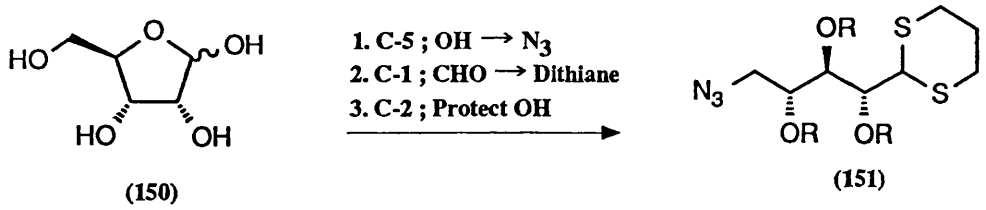
Part 1. Introduction

Having established in chapters 2 and 3 that the intramolecular azide cycloaddition reaction of ketene thioacetals can be used for synthesis of cyclic α-amino acids, we wished to demonstrate the synthetic potential of this reaction by the synthesis of a ring-substituted proline (**147**) (Scheme 75). We hoped that we would be able to introduce the substituents into the pyrrolidine ring by preparing a suitably substituted cyclisation precursor (**142**), as briefly mentioned in the previous chapter. The problem of controlling the C-2 stereochemistry would also need to be addressed at this point. Hydrolysis of the α-aminoketene thioacetal (**145**) or reduction of the cyclic imine (**143**) are reactions which provide scope for relative asymmetric induction, while reduction of (**143**) also allows the possibility of using a chiral reducing agent to introduce asymmetry.

We chose as our target the known compound (2S, 3S, 4R)-3,4-dihydroxyproline (**148**), which has previously been prepared in racemic form from dehydroproline[154] and in optically active form from D-glucose[155]. A retrosynthetic analysis of (**148**) is given in Scheme 76. The ketene thioacetal present in the acyclic precursor (**149**) is disconnected in three ways leading eventually to the three carbohydrate starting materials, D-ribose, 2-deoxyribonolactone and D-erythrose. Of these starting materials, D-ribose and D-erythrose are readily available while 2-deoxyribonolactone is not. Two approaches to the target molecule (**148**) will be described, one from D-ribose and the other from D-erythrose.

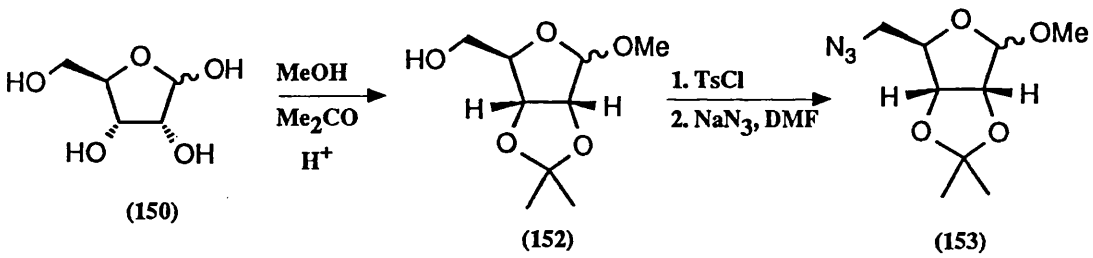


SCHEME 77.



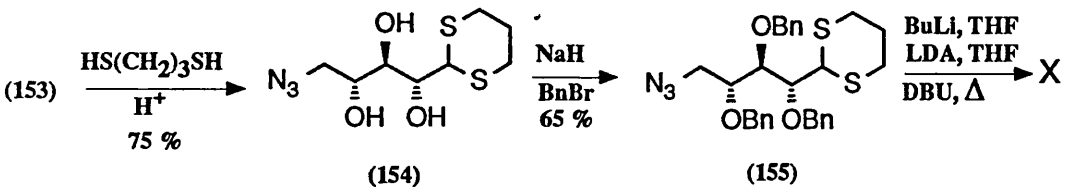
(150) (151)

SCHEME 78.



(150) (152) (153)

SCHEME 79.



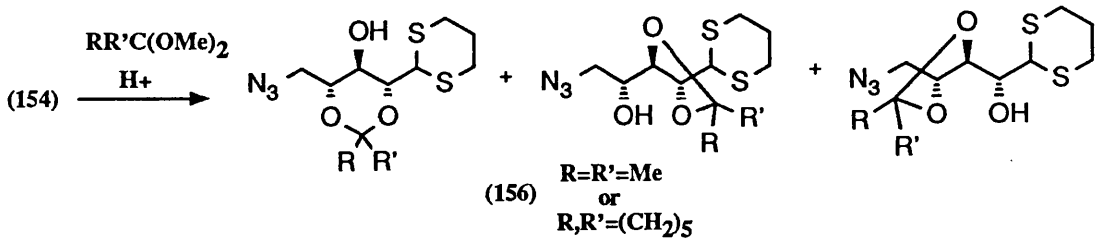
(154) (155)

SCHEME 80.

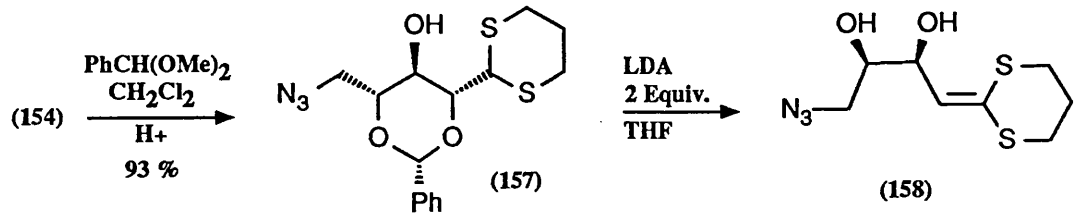
Part 2. D-Ribose as Starting Material

The preparation of ketene thioacetal (**149**) from D-ribose (**150**), as shown in the retrosynthetic analysis, exploits the base-induced elimination of an alkoxide from an α-alkoxy-1,3-dithiane. There are various reports of this process in the literature and, in each case, the alkoxide forms part of an acetonide protecting group[156] (Scheme 77). Our target was, therefore, the dithiane (**151**) which required three different manipulations of D-ribose, namely conversion of the primary alcohol to an azide, protection of the aldehyde as a dithiane and protection of the C-2 hydroxyl group as an ether (Scheme 78). Protection of the C-3 and C-4 hydroxyl groups may also be necessary.

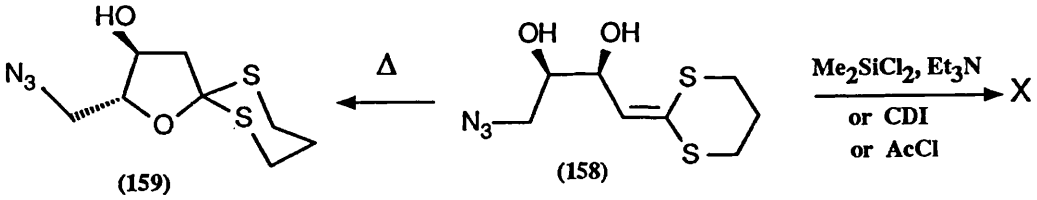
Conversion of the C-5 hydroxyl group to an azide required a suitably protected form of D-ribose, and a search of the literature revealed that this process is known. Treatment of (**150**) with methanol, acetone, 2,2-dimethoxypropane and HCl gave (**152**) in which all hydroxyl groups, except the primary one, are protected[157]. Tosylation of the primary alcohol[158] followed by azide displacement[159] gave compound (**153**) in approximately 50% overall yield (Scheme 79). Our next goal was to introduce the dithioacetal by treating the acetal (**153**) with propane-1,3-dithiol. A variety of techniques is available for this process[160] but none of the methods tried selectively replaced the methylfuranoside of (**153**) while leaving the acetonide intact. Best results were obtained by treating (**153**) with 2 equivalents of propane-1,3-dithiol in the presence of *p*-toluene sulphonic acid (PTSA), which gave triol (**154**) in 75% yield (Scheme 80). Selective protection of the C-2 alcohol in a form suitable for the elimination proved to be a somewhat arduous task. Our initial approach was to form the tribenzyl derivative (**155**) by treatment of triol (**154**) with sodium hydride and benzyl bromide. Unfortunately, when a solution of (**155**) in THF was treated with *n*-butyl lithium, none of the desired ketene thioacetal was formed and TLC revealed only baseline products. LDA had the same effect, while (**155**) was unreactive towards



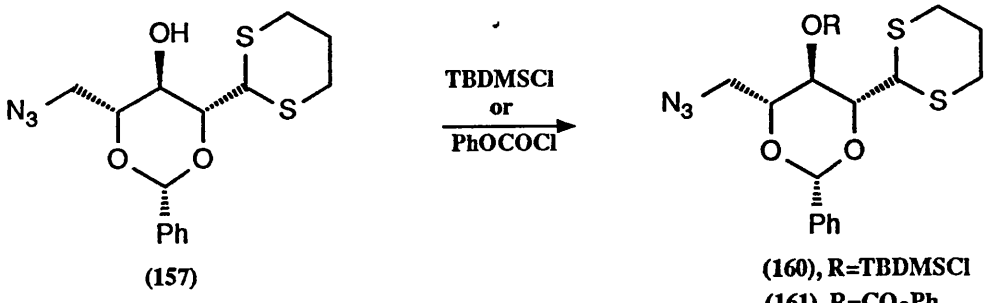
SCHEME 81.



SCHEME 82.



SCHEME 83.

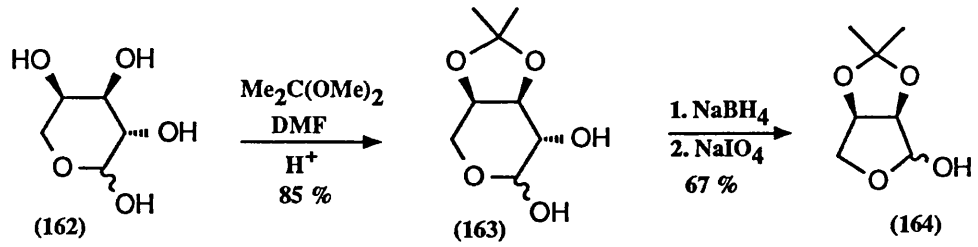


SCHEME 84.

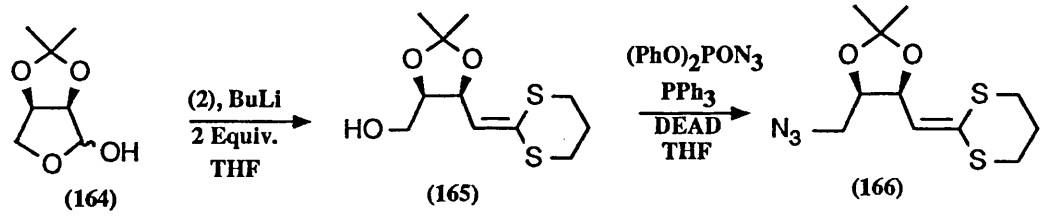
DBU. The polar product(s) observed may result from attack of the azide by *n*-butyl lithium[161], or removal of a benzyl proton followed by [1,2] Wittig rearrangement[162].

Since the benzyl protecting group proved unsuitable for our needs, alternative protecting groups were tried. Triol (**154**) reacted with either 2,2-dimethoxypropane or 1,1-dimethoxycyclohexane to give mixtures of acetals (**156**) which could not be separated (Scheme 81). This is not surprising since none of the structural isomers (**156**) is particularly favoured or disfavoured in terms of steric interactions. In contrast, the triol (**154**) reacted with dimethoxyphenylmethane to give only one compound (**157**), in which the 1,3-diol function present in (**154**) has been selectively protected (Scheme 82). This acetal is favoured over the other five possible products, since all four substituents of the 1,3-dioxane ring of (**157**) are equatorial which means that steric interactions will be minimized.

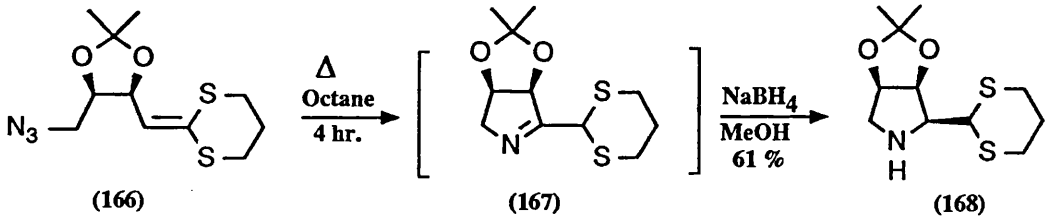
Treatment of dithiane (**157**) with two equivalents of LDA led cleanly to the desired diol (**158**) which was isolated in 73% yield. The reaction was less clean with *n*-butyl lithium. Thus far we had achieved our goal of preparing the substituted cyclisation precursor (**158**) from D-ribose, in a small number of steps. Unfortunately, we were unable to take this route any further since compound (**158**) proved to be unstable. Thermolysis of the unprotected diol gave a number of products, the main one being the dithioortholactone (**159**) which was isolated in 21% from one thermolysis experiment. Attempts to protect the diol were also in vain; dichlorodimethylsilane, carbonyl diimidazole and acetyl chloride each gave less polar compounds which could be observed by TLC but were unstable, and reverted to the diol (**158**) or other products on work-up (Scheme 83). We also protected the C-3 hydroxyl group of (**157**) both as the *tert*-butyldimethylsilyl ether (**160**) and as the phenyl carbonate (**161**) but having done this, the dithiane then resisted deprotonation (Scheme 84). The resistance towards deprotonation of (**160**) and (**161**) may be due to



SCHEME 85.



SCHEME 86.



SCHEME 87.

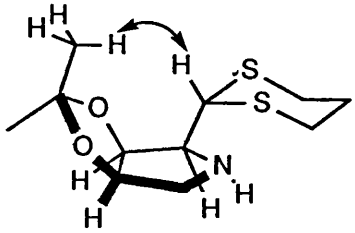


Figure 4.

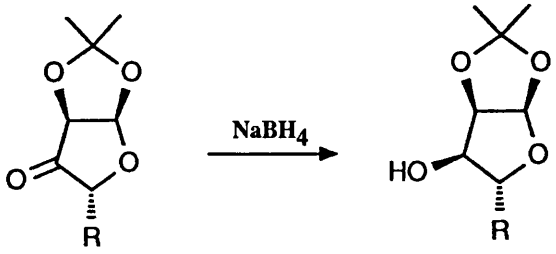
increased steric bulk around the dithiane C-2 position, or may reflect the fact that double deprotonation of (**157**) relied on a complex-induced proximity effect[227]. At this stage the synthesis based on D-ribose was abandoned and we decided that in our next approach, the C-3 and C-4 hydroxyl groups should be protected before installing the ketene thioacetal function.

Part 3. D-Erythrose as Starting Material

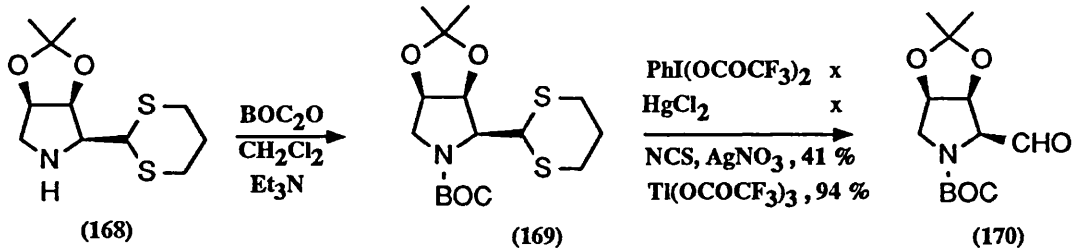
The retrosynthetic analysis given in Scheme 76 shows that the Peterson olefination disconnection of the ketene thioacetal leads to a derivative of D-erythrose. The protected form, 2,3,-O-isopropylidene erythrose (**164**), is available from cheap carbohydrate precursors by a number of routes and we chose D-arabinose[162] as the starting material. Selective protection of D-arabinose was achieved using 2,2-dimethoxypropane in DMF which led to the 3,4-O-isopropylidene derivative (**163**) in 85% yield[163] (Scheme 85). A one-pot procedure of reduction followed by oxidative cleavage then converted (**163**) to the desired D-erythrose derivative (**164**)[164]. This provided a concise route to reasonably large amounts of (**164**).

With the erythrose derivative (**164**) in hand, we were then able to construct the cyclisation precursor in two further steps. Peterson olefination of the lactol using two equivalents of dithiane derivative (**2**) gave the hydroxy ketene thioacetal (**165**) in 78% yield (Scheme 86). The hydroxyl group was converted cleanly to the azide using diphenylphosphoryl azide, which gave (**166**) in 85% yield. The intermediate (**165**) was best used immediately, since it cyclised to the corresponding dithioortholactone under acidic conditions.

Thermolysis of the azido ketene thioacetal (**166**) in refluxing octane led cleanly to a new compound after four hours. This was assumed to be cyclic imine (**167**) but the thermolysis product was not isolated. Addition of methanol and sodium

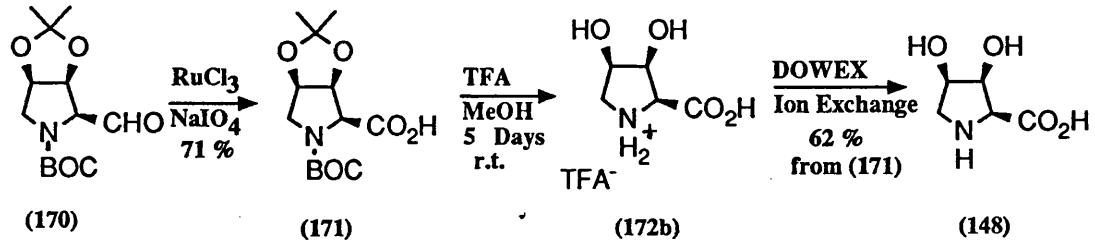


SCHEME 88.



(168) (169) (170)

SCHEME 89.

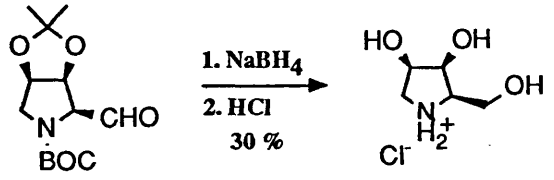


(170) (171) (172b) (148)

SCHEME 90.

borohydride at 0°C led to the pyrrolidine (**168**) in 61% yield from the azide (**166**) (Scheme 87). Only one diastereomer was isolated and the C-2 stereochemistry was confirmed by NOE enhancements, in particular from the protons of one dioxolane methyl group to the dithiane C-2 proton (Fig. 4). The stereochemical outcome of the reduction probably results from the steric bulk of the acetonide protecting group, which shields one face of the imine. Bicyclo[3.3.0]octanes, of which imine (**167**) is an example, react predominantly on the "exo" face rather than the "endo" face and a related example from the literature is shown in Scheme 88[165]. In terms of stereoelectronic factors, the observed product is predicted by the theory of Anh[166], while Cieplak's theory[167] favours formation of the unobserved C-2 epimer. It is unlikely, however, that stereoelectronic factors are significant in this case since the steric bias is so large.

In the process of converting the azide (**166**) to the pyrrolidine (**168**), we had achieved both the goals set out at the beginning of this chapter, i.e. introduction of substituents into the ring and control of the stereochemistry at C-2. To complete the synthesis of our target molecule (**148**), we needed to convert the dithiane group to a carboxylic acid without loss of stereochemical integrity at C-2. We decided to protect the secondary amine as the BOC derivative (**169**), which was a highly crystalline compound. Hydrolysis of the dithiane group of (**169**) proved to be the hardest step in the synthesis, possibly because the resulting aldehyde was unstable. Mercuric chloride[168] gave none of the desired aldehyde whereas N-chlorosuccinimide in the presence of silver nitrate[169] gave up to 41% of aldehyde (**170**) but the reaction was unreliable and yields were often lower than this. Bis (trifluoroacetoxy)iodobenzene[151] was also unsuccessful in this context but we eventually succeeded in the dithiane hydrolysis by using thallium tris(trifluoroacetate)[170] in moist ether. This reagent led cleanly to aldehyde (**170**) which could be purified by flash chromatography and was isolated in up to 94% yield (Scheme 89). We were aware at this stage that epimerization could occur at C-2, but



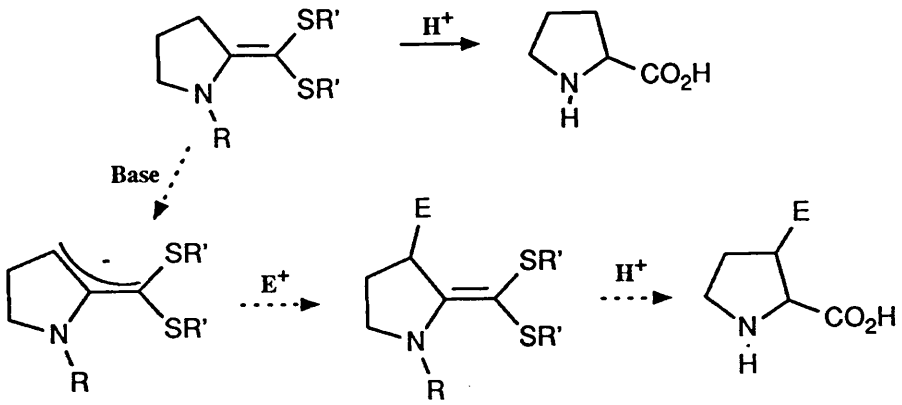
(170) (173b)

SCHEME 91.

we decided to convert aldehyde (**170**) to the final product and establish the stereochemistry at the end rather than concerning ourselves with each intermediate. Oxidation of (**170**) with ruthenium tetroxide[152] proceeded in 71% yield to give the acid (**171**) (Scheme 90). The BOC group was removed cleanly by stirring (**171**) in trifluoroacetic acid (TFA) at room temperature for one hour, but under these conditions the acetonide remained intact. Hydrolysis of both the BOC group and the acetonide could be achieved simultaneously by adding a small amount of water or methanol to the TFA[171]. Best results were obtained using TFA and methanol (10:1) which gave the deprotected amino acid as the TFA salt (**172b**) after five days at room temperature. Purification of (**172b**) by ion exchange chromatography gave the free amino acid (**148**) in 62% yield from (**171**).

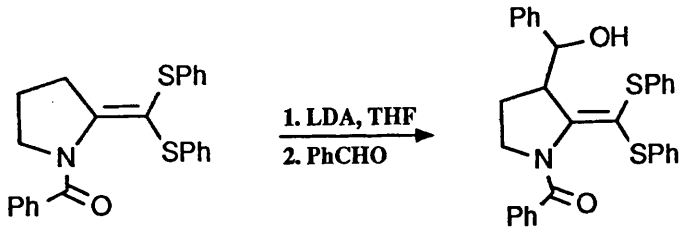
The stereochemistry at C-2 remained intact, as established by comparing spectroscopic data; the ^{1}H and ^{13}C NMR data of compound (**171**) were in close agreement with those reported.[155] Additionally, the spectroscopic data of (**171**) differed from those reported by the C-2 epimeric compound, (2R, 3S, 4R)-3,4-dihydroxyproline, the structure of which has been confirmed by X-ray crystallography.[172] The stereochemical assignment of aldehyde (**170**) was also supported by the fact that reduction with sodium borohydride followed by deprotection, gave the known pyrrolidine (**173b**) which is a glycosidase inhibitor[155]. (Scheme 91)

CHAPTER 5



(174) (175) (176)

SCHEME 92.



(117) (177)

SCHEME 93.

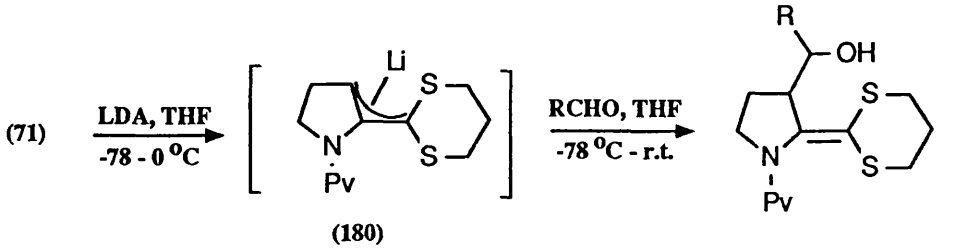
CHAPTER 5

3-Substituted Prolines from Sulphur-Stabilised Allylic Anions

Part 1. Introduction and Choice of Starting Material

The previous chapter described a method for the synthesis of substituted prolines, in which the substituents were introduced into the carbon skeleton before the cycloaddition reaction was carried out. This chapter describes an alternative strategy for the synthesis of substituted prolines, in which the substituents were introduced after construction of the pyrrolidine ring. In this way, a number of different proline derivatives were prepared from a common precursor, which thus represents a novel proline synthon.

Having prepared a number of cyclic α-aminoketene thioacetals, and demonstrated that they could be hydrolysed to give proline derivatives, we wondered, whether deprotonation at C-3 would be possible for any of these compounds. If so, this would give the sulphur stabilised allylic anion (**174**) which may, under certain conditions, be viewed as synthetically equivalent to a homoenolate of proline (Scheme 92). Alkylation at the γ-position would give adduct (**175**) which, on hydrolysis of the ketene thioacetal, would give the 3-substituted proline (**176**). We were concerned that alkylation of the allylic anion (**174**) might also occur at the α-position and so our first substrate for this study was S,S′-diphenyl derivative (**117**). Bulky sulphur substituents, including isopropyl and phenyl groups, are known to favour γ-alkylation[173] while dithiane derivatives usually give α-alkylated products[174]. Addition of (**117**) to a freshly prepared solution of LDA in THF, followed by addition of benzaldehyde, gave the γ-adduct (**177**) in 23% yield (Scheme 93). Only one diastereomer was observed, but no attempt was made to establish the relative stereochemistry of the two chiral centres in (**177**). The alkylation was also



SCHEME 94.

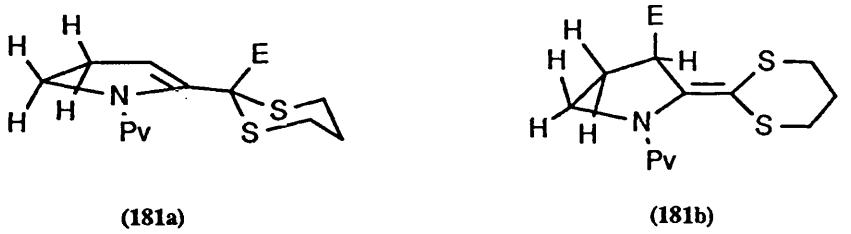
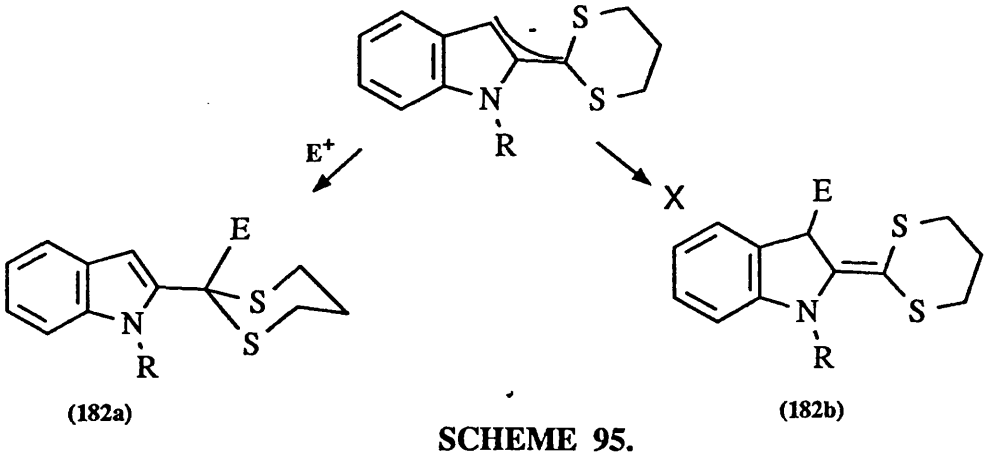


Figure 5.



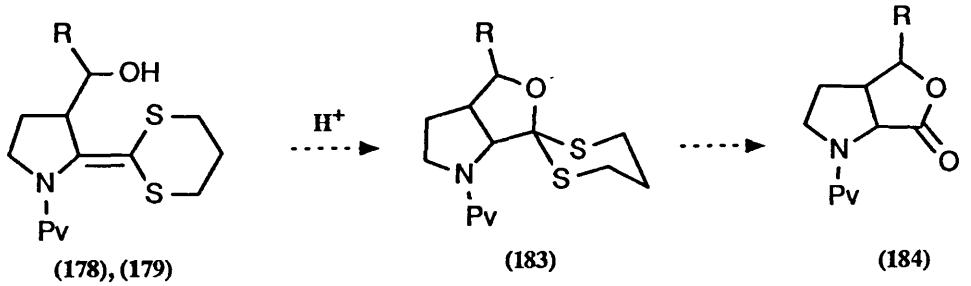
SCHEME 95.

attempted using methyl iodide and benzyl bromide as electrophiles, but no alkylation products were isolated. Because of this fact, as well as the high molecular weight of **(117)** and low yields associated with its preparation, no further alkylation reactions were attempted with this substrate.

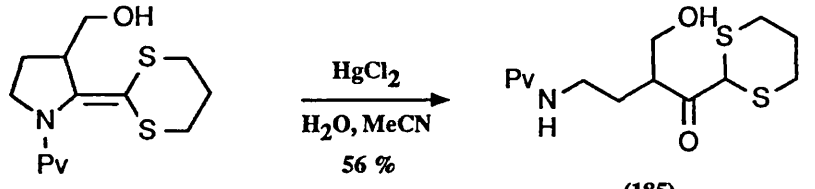
After the limited success of the S,S'-diphenyl derivative **(117)**, we decided to try some alkylations using a more readily available ketene thioacetal. We chose the N-pivaloyl derivative **(71)** because it can be prepared either by the cycloaddition process or directly from proline. In addition, compound **(71)** is crystalline so it can be obtained with a high degree of purity and is more easily handled.

Our initial alkylation experiments were performed using benzaldehyde and formaldehyde as the electrophiles. Both aldehydes led cleanly to γ-adducts **(178)** and **(179)**, respectively (Scheme 94). These results show that the allylic anion is formed efficiently using LDA as base. Deprotonation occurred slowly at low temperatures and after a number of experiments, the following procedure was adopted; a freshly prepared solution of LDA in THF was cooled to -78°C then a solution of **(71)** in THF was added. The solution was allowed to warm to 0°C over approximately 30 minutes and then the temperature of the reaction flask was maintained between -20°C and 0°C for a further hour. The resulting solution of the allylic anion **(180)**, which had a pale yellow colour, was then cooled to -78°C and treated with a solution in THF of the appropriate electrophile. The reaction mixture was allowed to warm to room temperature, stirred for a further hour and then quenched.

The formation of aldehyde adducts **(178)** and **(179)** is interesting because no α-adduct was detected in either reaction mixture. Other electrophiles also gave exclusively γ-alkylation (*vide infra*). The preference for γ-alkylation observed in our system is curious because, as mentioned above, allylic anions prepared from dithiane derivatives usually give a high proportion of α-alkylated products. This selectivity is

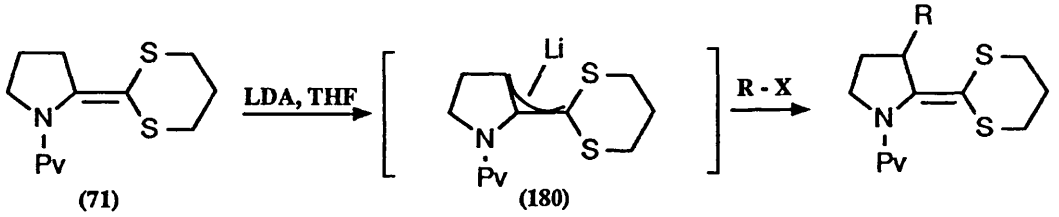


(178), (179) (183) (184)



(179) (185)

SCHEME 96.



(71) (180)

SCHEME 97.

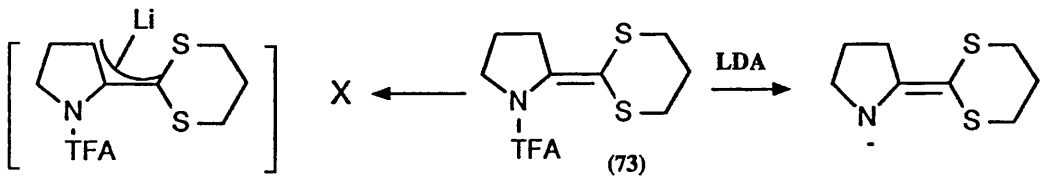
Electrophile	R	Product	Yield
Allyl bromide	Allyl	(188)	66%
$PhCH_2Br$	$PhCH_2$	(189)	86%
MeI	Me	(186)	49%
$^nC_3H_7I$	^{n}Propyl	(187)	72%
$(CH_2O)_n$	CH_2OH	(179)	82%
PhCHO	CH(Ph)OH	(178)	55%
Cl-CO_2Me	CO_2Me	(190)	85%
$BrCH_2CO_2Et$	CH_2CO_2Et	(191)	64%

Table 2.

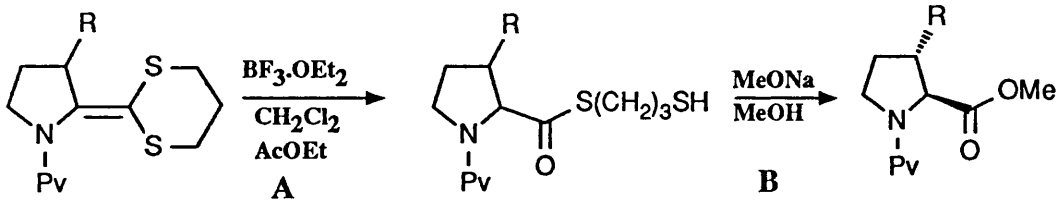
thought to arise from the fact that more charge resides at C-α of the allylic anion than at C-γ, due to the charge-stabilising effect of the sulphur atoms. Steric interactions between the electrophile and the dithiane ring are small, so that α-alkylation is favoured, but larger sulphur substituents cause the steric factor to dominate resulting in γ-alkylation. In the case of allylic anion (**180**), the preference for γ-alkylation can be explained in terms of ring strain in the product[175]. α-Alkylation would lead to (**181a**) (Figure 5) in which the pyrrolidine ring contains three adjacent sp_2 atoms. The ring would be planar resulting in unfavourable eclipsing of the two methylene units. In contrast, the γ-alkylated product (**181b**) has only two sp_2 atoms and so puckering can occur to relieve 1,2-interactions in the ring. A related allylic anion, prepared by Husson and co-workers, underwent alkylation only at the α-position to give (**182a**). In this case the α-selectivity was easily explained since the nitrogen-containing ring was part of an indole, so that alkylation at the γ-position to give (**182b**) would have led to loss of aromaticity[228](Scheme 95).

Returning to the alkylation products (**178**) and (**179**), we had hoped that rearrangement to the corresponding dithioortholactone (**183**) would be possible. Hydrolysis to the lactone (**184**) would then provide a means of controlling the relative stereochemistry at C-2 and C-3 (Scheme 96). Unfortunately we failed to achieve this goal, despite trying a variety of conditions. Treatment of (**179**) with mercuric chloride in aqueous acetonitrile led to the amino ketone (**185**) in 56% yield. Presumably mercuric chloride served only to generate HCl by hydrolysis to mercuric oxide (Scheme 96).

The allylic anion (**180**) reacted not only with aldehydes but also with a range of other electrophiles (Scheme 97). These included the alkyl halides, methyl iodide, *n*-propyl iodide, allyl bromide and benzyl bromide. Methyl chloroformate and ethyl bromoacetate also reacted cleanly, and in each case we only observed γ-alkylation. The results of the alkylation reactions are summarised in Table 2.



SCHEME 98.

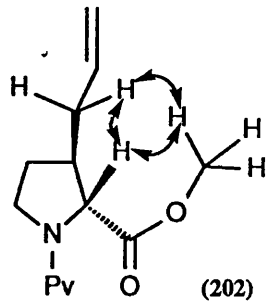


SCHEME 99.

Substrate	R	Yield A	Product	Yield B	Product
(188)	Allyl	88%	(196)	92%	(202)
(189)	$PhCH_2$	88%	(197)	79%	(203)
(186)	Me	75%	(194)	51%	(200)
(187)	*n*-Propyl	81%	(195)	69%	(201)
(179)	CH_2OH	21%	(192)	–	
(190)	CO_2Me	38%	(198)	–	
(191)	CH_2CO_2Et	46%	(199)	–	

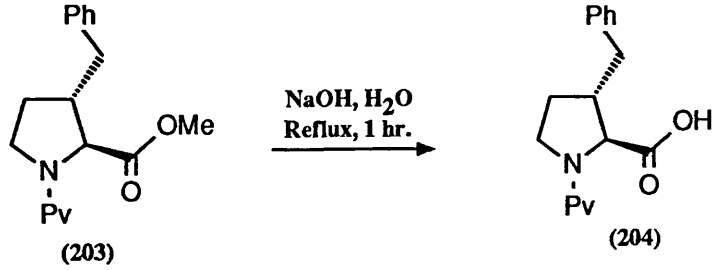
Table 3.

Figure 6.



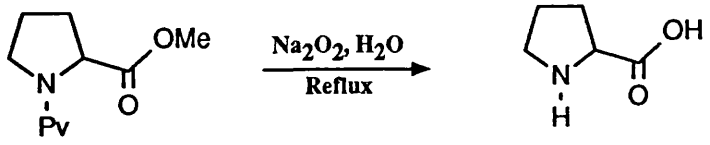
Having prepared a number of adducts, we were then faced with the task of hydrolysing these compounds to give the desired proline derivatives. As discussed in chapter 3, our initial attempts to hydrolyse the pivaloyl derivatives using conventional protic conditions led only to undesired amino ketones. Changing the nitrogen protecting group from pivalamide to trifluoroacetamide overcame the problem of hydrolysis but the ketene thioacetal (**73**) was not stable in the presence of lithium amide bases. Both LDA and lithium tetramethylpiperidide (LTMP) caused trifluoroacetamide cleavage rather than the desired deprotonation (Scheme 98). The problem of regioselective hydrolysis was eventually overcome by using excess boron trifluoride etherate, and this method was applied to the alkylation products (**178-9**) and (**186-91**). The method worked well for the 3-alkyl derivatives and gave good yields of the corresponding thioloesters (**194-197**) (Scheme 99). The yields were somewhat lower for the more highly functionalised adducts, but the thioloesters (**193**), (**198**) and (**199**) could be isolated nevertheless. In each case, ^{1}H NMR revealed substantially or purely one diastereomer to be present, but we did not attempt to assign the relative stereochemistry of the thioloesters. The 3-alkyl derivatives (**194-197**) could be converted to the corresponding methyl esters (**200-203**) by treatment with sodium methoxide in methanol at 0°C for 3 hours. These results are summarised in Table 3.

The protected proline derivatives (**200-203**) were isolated by chromatography, and 270MHz ^{1}H NMR revealed only one diastereomer to be present in each case. This does not discount the possibility that a small proportion of the other diastereomer is present in each case since NMR signals due to the minor component may be obscured by signals from the major component. It is also possible that the minor diastereomers were removed by chromatography. Based on literature precedent, *trans*-substituted proline derivatives are usually thermodynamically more stable than the corresponding *cis*-isomers[176], and the conditions used for transesterification are likely to cause equilibration to the thermodynamic product. In



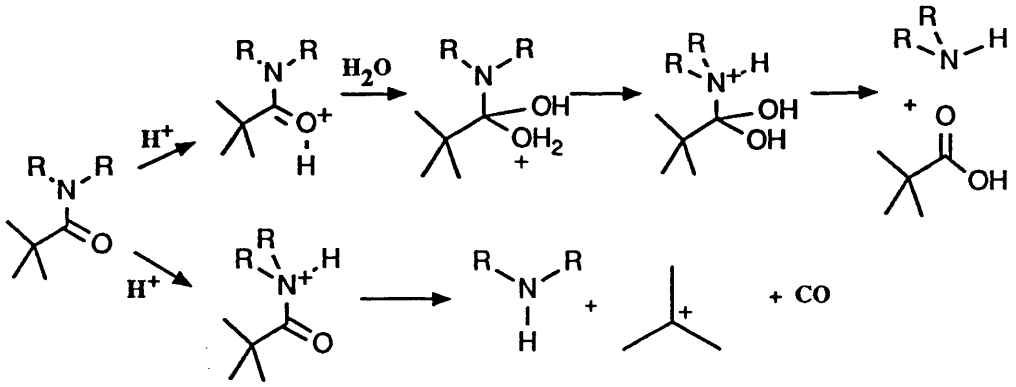
(203) (204)

SCHEME 100.

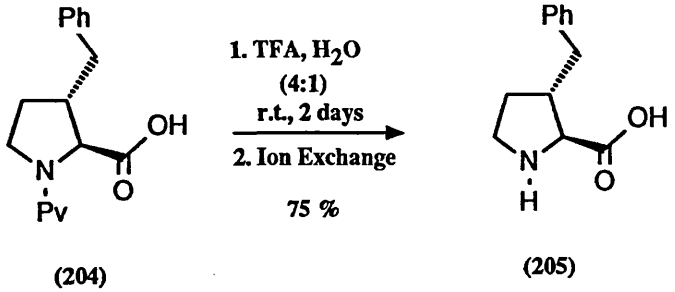


(93) Proline

SCHEME 101.



SCHEME 102.



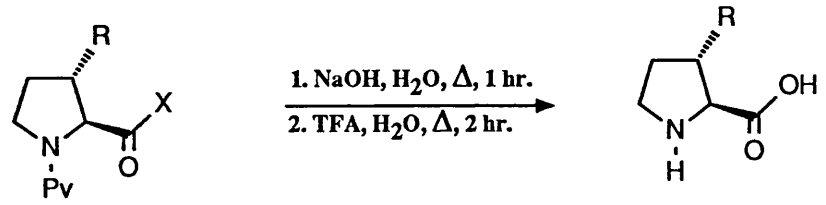
(204) (205)

SCHEME 103.

the case of the 3-allyl proline derivative (**202**), the stereochemical assignment was supported by NOE studies (Figure 6). We assume that the proline derivatives (**200**), (**201**) and (**203**) also have *trans*-stereochemistry.

Having prepared the 3-substituted proline derivatives (**200**)-(**203**), we wished to hydrolyse the acid and amine-protecting groups and thus to prepare the corresponding free amino acids. Amide hydrolysis is know to be difficult in many cases[140] but we did not anticipate problems with the ester hydrolysis. We chose the benzyl derivative (**203**) as our first substrate for deprotection. The methyl ester was readily cleaved with aqueous sodium hydroxide by heating under reflux for one hour, which gave the acid (**204**) in 80% yield, with little or no amide hydrolysis taking place (Scheme 100). Two specialized techniques for amide hydrolysis have been reported, one involving the use of more nucleophilic sodium peroxide[177], and the other using potassium *tert*-butoxide in aqueous THF[178]. We tried the sodium peroxide method on the unsubstituted proline derivative (**93**), and observed the formation of proline by TLC (Scheme 101), but this technique did not work for the benzyl derivative (**204**), possibly because of solubility problems. Prolonged heating of the reaction mixture caused corrosion of the reaction flask faster than amide hydrolysis! Acid hydrolysis of amides is usually slower than alkaline hydrolysis, but we wondered whether the pivalamide group might present itself as a special case. Protonation of amides occurs most readily on oxygen, but it can also occur on nitrogen[179]. This presents an alternative mechanism for the hydrolysis of pivalamides, involving fragmentation of N-protonated species (Scheme 102). Which ever mechanism may be correct, stirring the amide (**204**) in aqueous TFA at room temperature for 2 days gave the amino acid (**205**) in 75% yield after purification by ion exchange chromatography (Scheme 103).

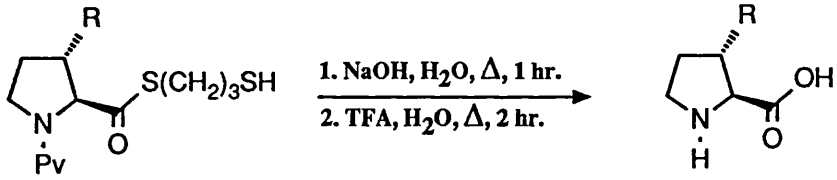
As far as we are aware, 3-benzyl proline has not been reported previously in the literature. However, 3-methyl proline and 3-*n*-propyl proline have been prepared[180].



(201), R=^{n}Prop, X=OMe
(194), R=Me, X=$S(CH_2)_3SH$

(206), R=^{n}Prop
(207), R=Me

SCHEME 104.



(198), R=CO_2Me
(199), R=CH_2CO_2Et

(208), R=CO_2H
(209), R=CH_2CO_2H

SCHEME 105.

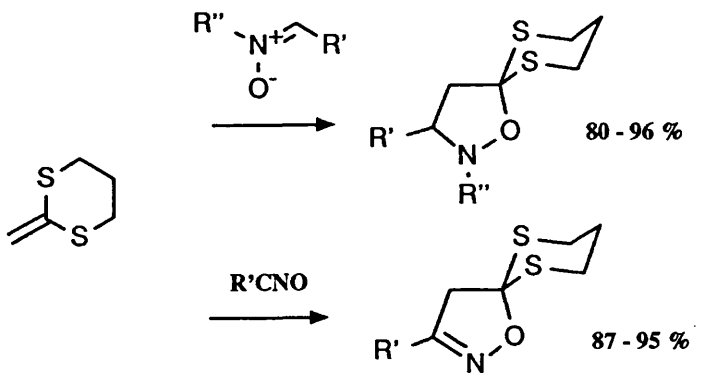
Treatment of the *n*-propyl derivative (**201**) with aqueous sodium hydroxide followed by aqueous TFA gave amino acid (**206**) in 89% yield as a the pure *trans* isomer. The amide hydrolysis was complete after 2 hours heating under reflux. 3-Methyl proline (**207**) was prepared using a more direct approach by treating the thioloester (**194**) to the same conditions of base followed by acid (Scheme 104). The resulting amino acid was isolated as a mixture of *cis* and *trans* compounds (ratio 1:10.2). The spectral data for compounds (**206**) and (**207**) matched the data from the literature. In both cases the major isomer observed by us had been assigned as *trans* by the previous workers.

As mentioned above, the esters (**190**) and (**191**) were hydrolysed by boron trifluoride to give the corresponding thioloesters (**198**) and (**199**) respectively. Treatment of these thioloesters with sodium methoxide gave none of the expected diesters, possibly because the reaction was complicated by the formation of acid anhydrides. Fortunately we were able to make use of thioloesters (**198**) and (**199**) by sequential treatment with sodium hydroxide and aqueous TFA. This two step procedure involved three functional group interconversions, and led to the amino acids (**208**) and (**209**) which were purified by ion exchange chromatography (Scheme 105). Unfortunately, the free amino acids (**208**) and (**209**) proved difficult to handle and we were not able to recrystallise them, despite the fact that ^{1}H NMR indicated a high degree of purity. The free amino acid (**209**) has been reported previously[214], as has a derivative of (**208**)[177]. These proline derivatives represent conformationally restricted variants of the naturally occurring amino acids, aspartic acid and glutamic acid. Rotation about the Cα-N and Cα-Cβ bonds is possible in the acyclic amino acids, but such rotation is severely restricted in the cases of (**208**) and (**209**). Conformationally restricted variants of naturally occurring amino acids have found use in the study of structure-activity relationships of peptides[212].

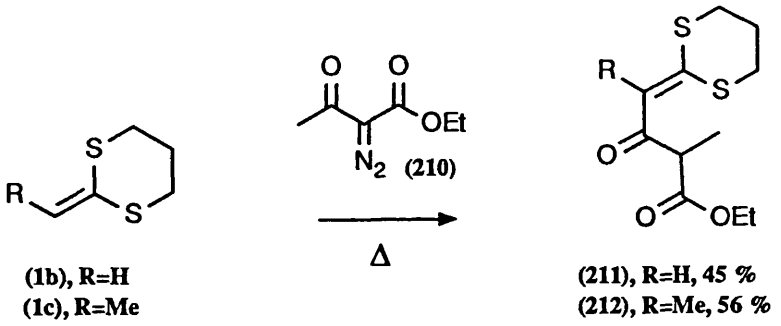
In summary, we have demonstrated that the α-aminoketene thioacetal (**71**) could be cleanly deprotonated to give the corresponding allylic anion (**180**), which

reacted with a range of electrophiles. Alkylation of (**180**) occurred exclusively at the γ-position and the alkylated products were hydrolysed to give 3-substituted prolines, demonstrating that the allylic anion (**180**) is synthetically equivalent to the homoenolate of proline.

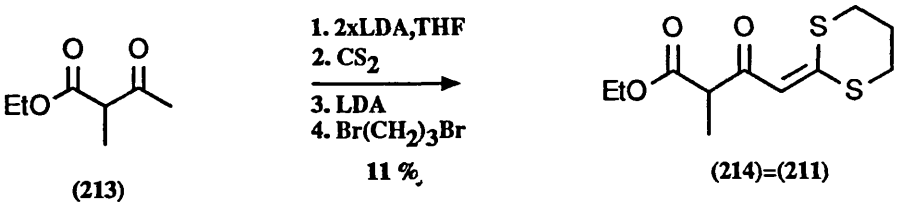
CHAPTER 6



SCHEME 106.



SCHEME 107.



SCHEME 108.

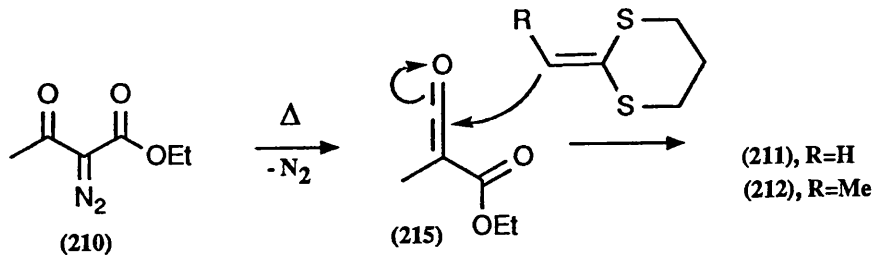
CHAPTER 6

Miscellaneous Results

Part 1. Ketene Thioacetals and Diazo Compounds

The results described in earlier chapters concern 1,3-dipolar cycloaddition reactions of ketene thioacetals in which the 1,3-dipole is an azide. Shortly after we began this work, a report appeared describing the efficient reaction of ketene thioacetal (**1b**) with both nitrile oxides and nitrones[181]. The products were isolated in high yield (Scheme 106). Wishing to further investigate the scope of ketene thioacetals as 1,3-dipolarophiles, we also studied their reactivity towards diazo compounds.

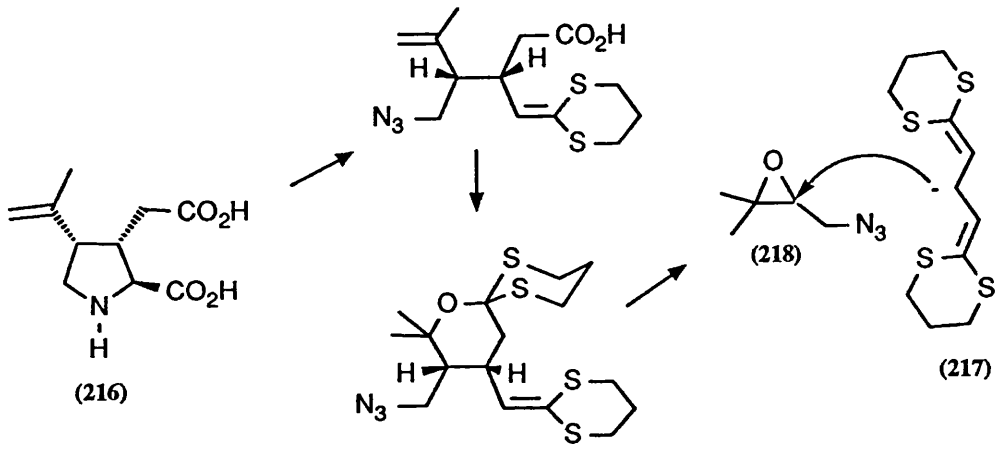
Ketene thioacetal (**1c**) was added to a freshly prepared solution of diazomethane[182], and the temperature of the reaction vessel was steadily increased from 0°C. Prolonged heating at 70-80°C gave no new products and (**1c**) was recovered unchanged. The yellow colour of diazomethane gradually disappeared from the reaction mixture, due to decomposition or evaporation. This low reactivity is explained by the relatively high energies of the frontier orbitals of both the 1,3-dipole[183] and, we assume, the 1,3-dipolarophile. The relatively electron-deficient ethyl diazoacetate[184] also failed to give cycloaddition products, and the major new compound isolated was apparently a polymerized product resulting from decomposition of ethyl diazoacetate. In contrast, ethyl acetodiazoacetate (**210**)[185] did react with ketene thioacetals (**1b**) and (**1c**) to give 1:1 adducts (**211**) and (**212**) respectively (Scheme 107). In these adducts, the carbon skeleton of (**210**) has undergone rearrangement and we took some time to deduce the structures of (**211**) and (**212**). Proof of the structure of compound (**211**) was obtained by an independent synthesis starting from ethyl acetopropionate (**213**). The dianion of (**213**) was treated with carbon disulphide, deprotonated again and then quenched with 1,3-dibromopropane (Scheme 108). This gave the ketene thioacetal



(210) (215)

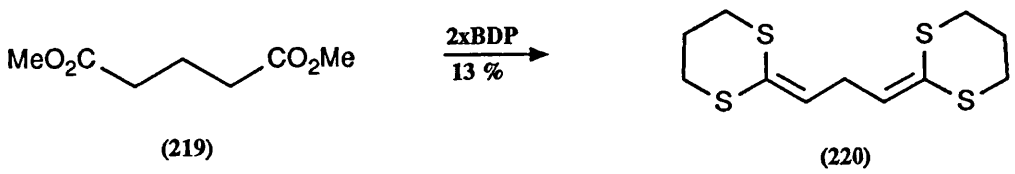
(211), R=H
(212), R=Me

SCHEME 109.



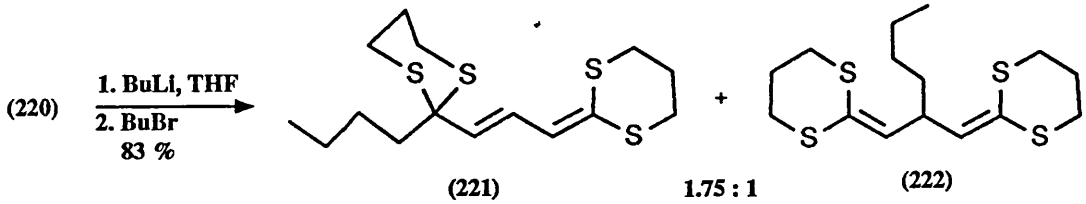
(216) (218) (217)

SCHEME 110.



(219) (220)

SCHEME 111.



(221) 1.75 : 1 (222)

SCHEME 112.

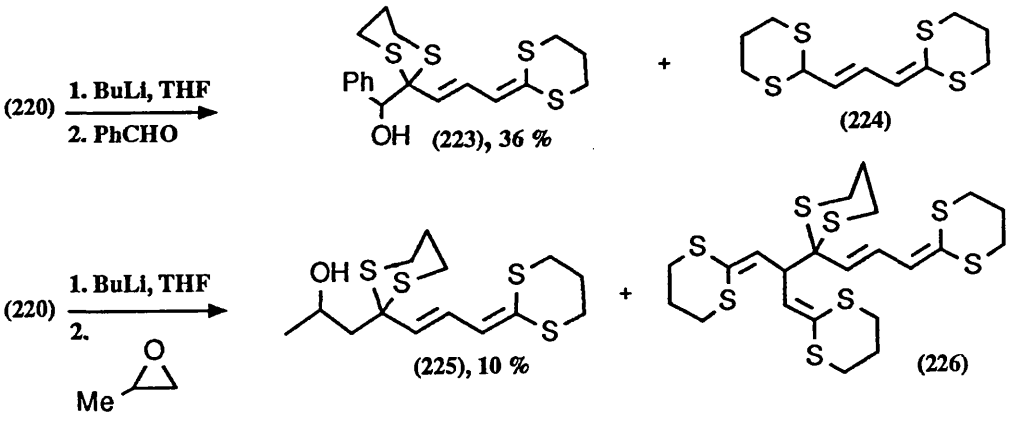
(**214**) which was isolated in 11% yield and was identical to (**211**). The structure of (**212**) was assigned by comparison of spectra with those of (**211**).

Having established the structures of 1:1 adducts (**211**) and (**212**), we then sought a mechanism which would explain their formation. We were disappointed to find that (**211**) and (**212**) probably do not arise from 1,3-dipolar cycloaddition, but rather from thermal decomposition of the diazo compound (**210**). Thermolysis of α-diazoketones such as (**210**) causes rearrangement with loss of nitrogen. In this case the rearrangement product is ketene (**215**), which acts as an acylating reagent towards ketene thioacetals (**1b**) and (**1c**) (Scheme 109). This rearrangement is known as the Wolff rearrangement[186]. We did not pursue our investigation of the reactivity of ketene thioacetals towards diazo compounds further than this point, nor did we investigate any other 1,3-dipoles.

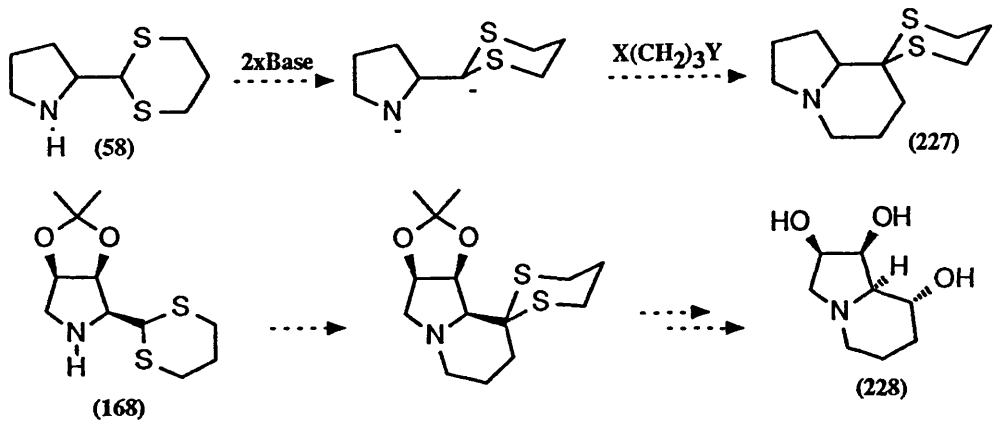
Part 2. A Novel Pentadienyl Anion

Chapter 2 described the synthesis of proline derivative (**52**) using the intramolecular azide cycloaddition reaction. We wondered whether we could apply this methodology to the synthesis of the substituted proline α-kainic acid (**216**). A retrosynthetic analysis of (**216**), leading to the pentadienyl anion (**217**) and epoxide (**218**), is given in Scheme 110. We decided to prepare the anion (**217**), and to investigate its reactivity towards various electrophiles.

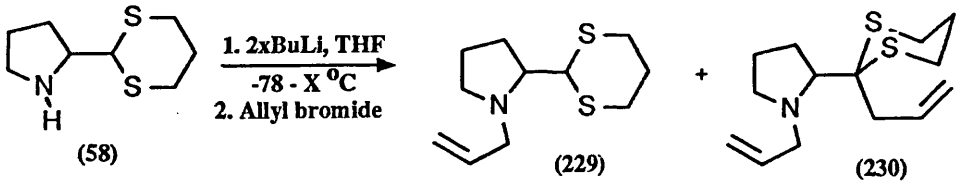
Dimethyl fumarate (**219**) was treated with two equivalents of BDP, which gave the desired bis(ketene thioacetal) (**220**) in 13% yield (Scheme 111). A solution of (**220**) in THF was treated with *n*-butyl lithium, which led to the desired anion (**217**). This anion was quenched with *n*-butyl bromide and the mixture of α- and γ-adducts (**221**) and (**222**) was isolated in 83% yield. The ratio of (**221**):(**222**) was 1.75:1, as judged by ^{1}H NMR (Scheme 112). When anion (**217**) was treated with benzaldehyde,



SCHEME 113.

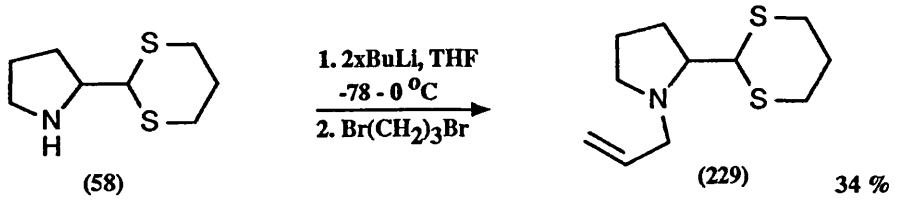


SCHEME 114.



Temp. X	(229)	(230)
-40 °C	43 %	0 %
0 °C	7 %	14 %

SCHEME 115.



SCHEME 116.

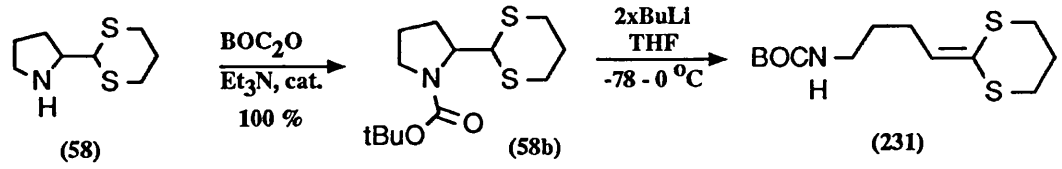
the α-adduct (**223**) was isolated in 36% yield in addition to the tautomer (**224**) of the starting material. Use of propene oxide as the electrophile gave only 10% of the α-adduct (**225**), in addition to the α,γ-dimer (**226**) of starting material (**220**) (Scheme 113). The formation of (**226**) is interesting but not unprecedented[187,188] and may be due to contamination of the reaction mixture by oxygen (from air) or peroxides (from THF).

We were disappointed but not particularly surprised that anion (**217**) gave only α-adducts with harder electrophiles, and this reactivity meant that our retrosynthetic analysis of α-kainic acid shown in Scheme 111 was no longer valid. Despite the fact that the proportion of γ-adducts obtained from sulphur stabilized allylic anions has be increased by changing a variety of conditions such as the electrophile[189], counterion[190], sulphur substituents[173,174], solvent and temperature[191], we did not develop this chemistry any further.

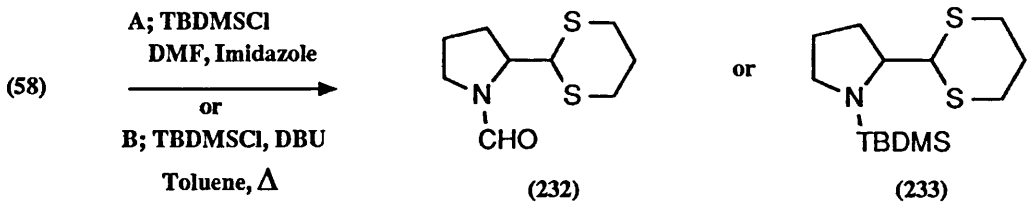
Part 3. Attempted Synthesis of Indolizidines

Reduction of the cyclic imine (**38**), formed by thermolysis of azide (**34**), led to pyrrolidine (**58**). We wondered whether deprotonation and subsequent alkylation of (**58**) would provide a route to indolizidines *via* compound (**227**) (Scheme 114). In particular, the more highly functionalised pyrrolidine (**168**) would then represent an advanced intermediate for the synthesis of swainsonine (**228**).

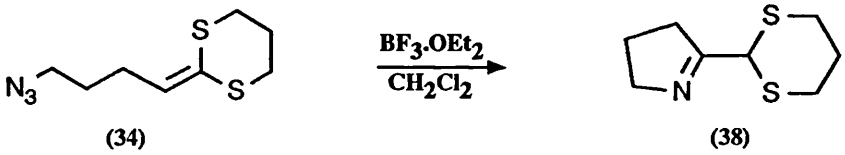
Treatment of (**58**) with two equivalents of *n*-butyl lithium at low temperature, followed by excess allyl bromide, gave only the N-alkylated pyrrolidine (**229**) (Scheme 115). Presumably, formation of the required dianion does not take place at -40°C, but when the experiment was repeated with warming of the reaction mixture to 0°C before quenching, a mixture of N-alkylated compound (**229**) and N,C-dialkylated compound (**230**) was produced. This demonstrates that we were able



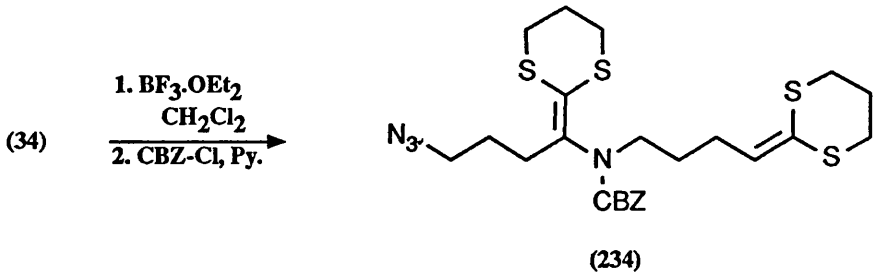
SCHEME 117.



SCHEME 118.



SCHEME 119.



SCHEME 120.

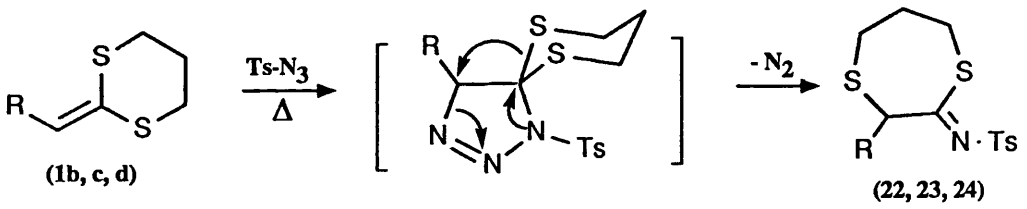
to form the desired dianion of (**58**), albeit with a low yield of dialkylated product. Attempts to carry out the annulation with dibromopropane gave none of the desired indolizidine (**227**), and the major product isolated was the N-allyl pyrrolidine (**229**). This presumably results from deprotonation of 1,3-dibromopropane to give allyl bromide (Scheme 116).

After our limited success with dianion formation, we decided to protect the secondary amine group present in (**58**) and then to attempt deprotonation and alkylation of the dithiane group. Protection of the amine with the electron-withdrawing BOC group gave carbamate (**58b**). Deprotonation of (**58b**) with *n*-butyl lithium gave, not surprisingly, the ketene thioacetal (**231**), resulting from fragmentation of the dithianyl anion or a direct E2 elimination (Scheme 117). Treatment of amine (**58**) with *tert*-butyldimethylsilyl chloride under standard conditions[192] gave the N-formyl derivative (**232**). Modified conditions[193] gave the desired silylated amine (**233**) (Scheme 118) but attempts to alkylate (**233**) were unsuccessful and we abandoned our approach to indolizidines at this stage.

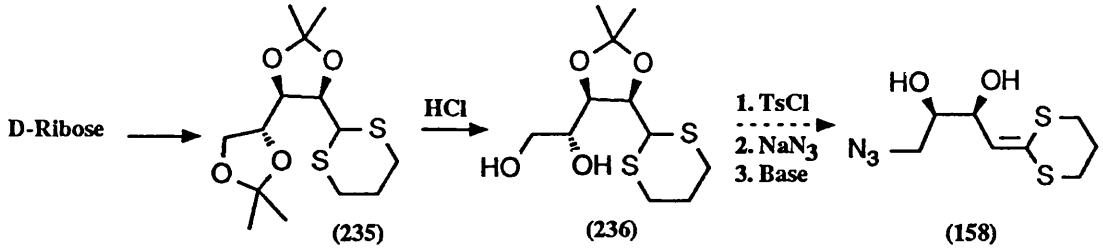
A closely related and more successful approach to indolizidines has recently been reported[194]. Two approaches to the indolizidine skeleton based on azide cycloaddition reactions were described earlier[136a, 136d].

Part 4. Lewis Acid Catalysed Azide Decomposition

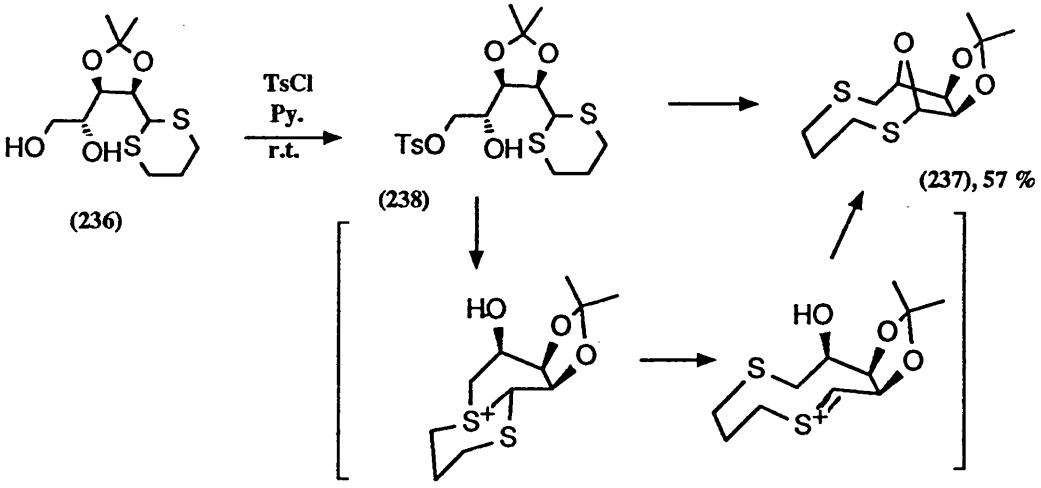
Alkyl and aryl azides are decomposed by Lewis acids such as antimony pentachloride[195], aluminium trichloride[196] and boron trifluoride[197]. Intramolecular reactions of azidoboranes are also known[198, 199], and lead to nitrogen heterocycles. Inspired by these reports, we treated the azide (**34**) with boron trifluoride etherate in dichloromethane at 0°C. This led to a new compound identified by TLC as the cyclic imine (**38**) (Scheme 119). We were excited by this initial result, which suggested that



SCHEME 121



SCHEME 122.



SCHEME 123.

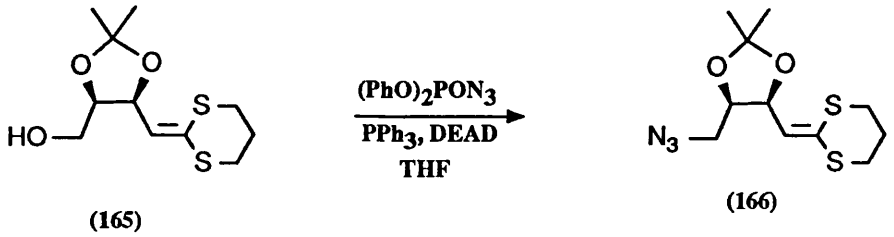
the cyclisation reaction, previously performed in *n*-octane, could actually be carried out at room temperature or below, but unfortunately we were not able to reproduce this reaction. However, when the azide (**34**) was treated first with boron trifluoride etherate and then with benzyl chloroformate and pyridine, the major product was found to be the dimer (**234**) arising from intermolecular reaction between the ketene thioacetal and the azide-boron complex (Scheme 120). These preliminary results were not investigated in more detail.

Part 5. Sulphur Participation and Migration

This section describes some reactions in which the simultaneous presence within a molecular of a sulphur atom and a developing positive charge led to some unexpected products. Examples of sulphur participation in nucleophilic displacement reactions are too numerous to permit a thorough coverage. The subject was reviewed in 1963[200] and examples continue to appear in the literature[201,202], so perhaps one should not really regard sulphur participation as surprising or unexpected.

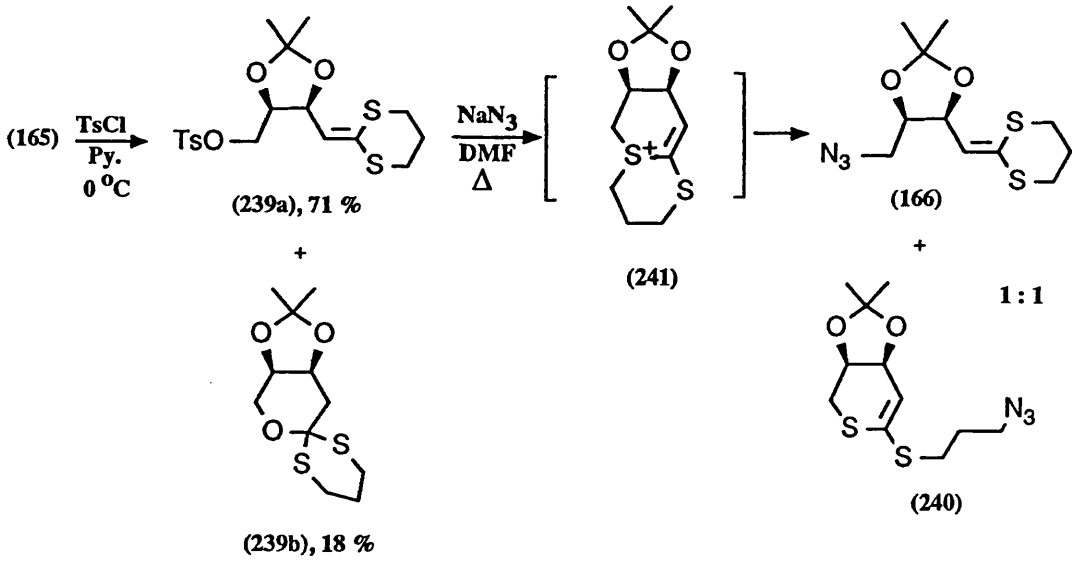
The first example of sulphur migration encountered in this study was described in chapter 1. 1,3-Dipolarcycloaddition reactions of tosyl azide and ketene thioacetals (**1b**) (**1c**) and (**1d**) led to the ring-expanded products (**22**), (**23**) and (**24**) respectively (Scheme 121). In this case, sulphur migration was assisted by both a positive charge and a negative charge. The remaining examples of sulphur participation included in this section have not been described in previous chapters.

During our attempted synthesis of (2S, 3S, 4R)-3,4-dihydroxyproline (**148**) from D-ribose, we prepared the diol (**236**) by selective hydrolysis of the bis-acetonide (**235**), itself prepared from D-ribose in two steps[210,220] (Scheme 122). We intended to selectively convert the primary alcohol at C-5 to the azide, and then to carry out the base-induced acetonide fragmentation described in chapter 4. However, treatment of



(165) (166)

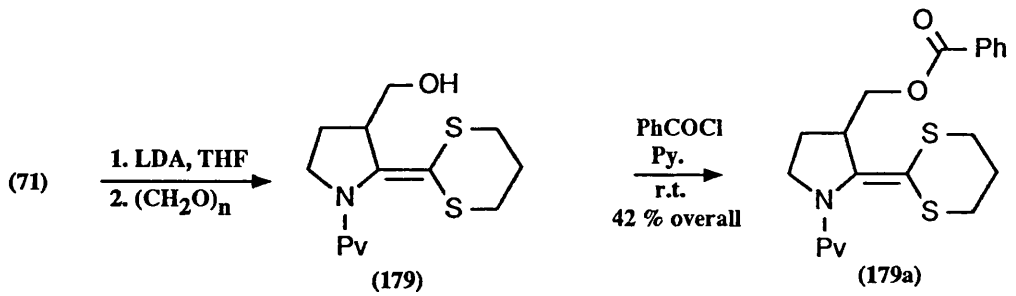
SCHEME 124.



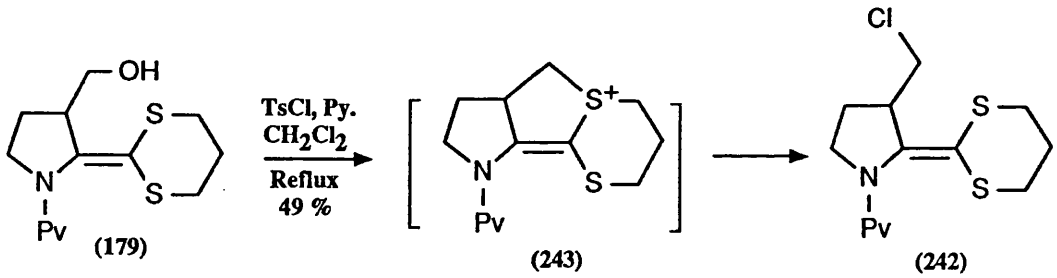
SCHEME 125.

diol (**236**) with tosyl chloride and pyridine at room temperature led not only to the expected tosylate but also to the rearranged product (**237**) which was isolated in 57% yield (Scheme 123). The tosylate (**238**) was stable enough to be isolated (10%) but rearranged slowly to (**237**), and attempted displacement with sodium azide gave only (**237**). Two diastereomers of (**237**) are possible but only one was isolated and we assume the stereochemistry to be as shown but this was not proved. The rearranged product (**237**) is thought to arise by displacement of the tosylate group by a sulphur lone-pair, followed by rearrangement of the resulting sulphonium ion. The participation of thioethers in tosylate displacements is well established[203].

Our more successful approach to 3,4-dihydroxy-proline (**148**) based on D-erythrose relied on the conversion of hydroxy ketene thioacetal (**165**) to the corresponding azide (**166**). This was achieved using diphenylphosphoryl azide, triphenyl phosphine and diethyl azodicarboxylate in THF at room temperature (Scheme 124)[135]. The mechanism of the Mitsunobu reaction still remains unclear[204,205] but the conversion of (**165**) to (**166**) must have involved activation at C-5, and fortunately this process occurred without sulphur participation when the reaction was performed at room temperature. However, our first approach to the conversion of (**165**) to (**166**) involved the two step procedure of tosylation followed by displacement with sodium azide. The tosylate (**239**) could be prepared in 71% yield from alcohol (**165**) and was quite stable at room temperature, unlike tosylate (**238**) described above. This difference in reactivity may be a reflection of the difference in nucleophilicity or spatial orientation of sulphur lone pairs in ketene thioacetals and dithioacetals. Despite the stability of tosylate (**239**) at room temperature, heating in DMF in the presence of sodium azide gave a 1:1 mixture of desired azide (**166**) and the rearrangement product (**240**) (Scheme 125). Presumably, the tosylate group is displaced by sulphur to give sulphonium ion (**241**) which reacts indiscriminately with azide, a demonstration of the reactivity-selectivity principle[206]. We were able to make use of the inseparable mixture of azides (**166**) and (**240**) simply by heating the mixture which effected the



SCHEME 126.



SCHEME 127.

desired cyclisation but left (**240**) unchanged. All the same we were pleased to discover an alternative reagent which overcame this undesired side reaction.

The final reaction described in this section also involved tosylation of an alcohol in the presence of a ketene thioacetal. The adduct of the allylic anion (**180**) and formaldehyde was described in the previous chapter. This alcohol (**179**) had a ^1H NMR spectrum which was more complicated than expected and so we wished to make a derivative of the alcohol, hoping that this would simplify the ^1H NMR spectrum. Treatment of (**179**) with benzoyl chloride and pyridine at room temperature for 24 hours gave the benzoate (**179a**) which did indeed have a much more simple spectrum (Scheme 126). However, treatment of alcohol (**179**) with tosyl chloride gave no new products at room temperature and so the reaction mixture was heated to reflux. This gave a new product which was isolated and found to be the chloride (**242**) (Scheme 127). Presumably, sulphur participation has occurred again to give the intermediate sulphonium ion (**243**) which was trapped by chloride. In this reaction, it is interesting to note that the intermediate was trapped selectively by the nucleophile, unlike (**241**) which gave a 1:1 mixture of products. This selectivity is probably a result of the ring strain present in (**243**), which means that the observed pathway is accompanied by a favourable relief of ring strain (i.e. release of energy).

The examples given above show how the participation of sulphur in reactions which involve developing positive charge can lead to rearranged products, mixtures of expected and unexpected products or simply to rate enhancement of displacement reactions.

EXPERIMENTAL SECTION

Instrumentation and Experimental Techniques

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}) with reference to the polystyrene 1601 cm^{-1} peak. Spectra of liquid samples were taken as thin films, or as solutions in chloroform ($CHCl_3$). Spectra of solid samples were taken as nujol mulls between sodium chloride discs.

Routine mass spectra from electron impact (E.I.) and chemical ionisation (C.I.) as well as high resolution accurate mass determinations were recorded with a VG Analytical 7070E instrument with a VG2000 data system. Chemical ionisation was performed with *iso*-butane as reagent gas. Where possible, the molecular ion peak (M^+) and base peak are indicated, as are all sizeable fragments.

Proton magetic resonance (^1H n.m.r.) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-23B and Varian Anaspect EM-360 spectrometers and at 270MHz on a Jeol GNM GX FT 270 spectrometer. Carbon 13 magnetic resonance (^{13}C n.m.r) spectra were recorded on a Jeol GNM GX FT 270 spectrometer operating at 67.8MHz and using 90 and 135 DEPT pulse sequences to aid in spectral assignment. ^1H and ^{13}C n.m.r. spectra were recorded in deuterochloroform ($CDCl_3$) deuterium oxide (D_2O) or hexadeuterodimethylsulphoxide (DMSO-D_6) as indicated and are expressed in parts per million (δ) downfield from internal tetramethylsilane or relative to HOD. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgetl 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light when possible and additionally by using a reagent which would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980. The most commonly used visualization reagents were phosphomolybdic acid (PMA), potassium permanganate, ninhydrin, vanillin and anisaldehyde.

Unless otherwise stated petrol refers to that fraction of petroleum spirit boiling in the range 60-80^{oC}. Solvents used as eluants in chromatography were dried and distilled prior to use.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 "flash" (Merck 9385) and 60H silica gel (Merck 7736) for reaction component seperations. A pressure gradient was developed using small, commercially available hand bellows (Gallenkamp). In all cases, where gradient elution was used, columns were prepared in the least polar solvent mixture and chromatography was carried out with this mixture as initial eluant, then by eluting with solvent mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the solid phase and applied as a thin layer to the top of the column or applied either neat or as a solution in the mobile phase.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous then redistilled and collected immediately prior to use. *n*-Butyl lithium was used as a solution in hexane

(1.6M), as supplied by Fluka. Lithium diisopropylamide was prepared immediately prior to use by treating a solution of diisoproplamine in dry THF under an atmosphere of nitrogen with 1 equivalent of *n*-butyl lithium at -20°C.

All other reagents and solvents were purified and dried when required using the methods described in D.D. Perrin, W.L.F. Armarego and D.R. Perrin, "Purification of Laboratory Chemicals", 2nd End., Pergamon Press, Oxford, 1980.

Glassware used for water sensitive reactions was baked in an over at 140°C for at least 12h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirrer bars were additionally flame-dried under a stream of dry nitrogen when appropriate. All air- and moisture-sensitive reactions were performed under an atmosphere of dry nitrogen.

In all experiments the excess solvent was removed with a Buchi rotary evaporator using a water aspirator at room temperature or with heating from a water bath. All yields quoted are of purified products and are uncorrected unless otherwise stated.

During work performed at I.C.I. Pharmaceuticals, C.I. mass spectra were recorded on a VG 12-12 or a VG 70-250 SE spectrometer using ammonia as reagent gas and ^1H n.m.r. spectra were recorded on a Bruker WM 200 instrument.

Preparation and use of bis(dimethylaluminium)propane-1,3-dithiolate (BDP)

This reagent was introduced by Corey[103] and is best prepared and used as follows; into a dried flask which has been flushed with nitrogen is added dichloromethane (20 ml) and trimethyl aluminium (2.0M in toluene, 10 ml, 20 mmol) by syringe. The reaction vessel is cooled to 0°C using an ice bath and propane-1,3-dithiol (1.0 ml, 10 mmol) is added dropwise by syringe. Care is exercised at this stage because the reaction is exothermic and methane gas is evolved. When the additon is complete the ice bath is removed and the solution is stirred for one hour which may result in precipitation of the reagent (depending on the ambient temperature). The ester (10 mmol) is then added as a solution in dichloromethane (20 ml) in one portion by syringe. The reaction is usually complete after stirring for 48 hours. Solvent is removed by rotary evaporation and the residual oil is diluted with ether (200 ml). Moist sodium sulphate is added by spatula which causes evolution of methane and precipitation of aluminium salts. The reaction is vigorous at first but becomes slower and is complete after 1.5-2 hours. The solution is filtered through sodium sulphate (anhydrous) and the residue washed with ether. The solvent is then removed by rotary evaporation and the product is purified by column chromatography or distillation.

1,3-Dithian-2-ylidene acetic acid ethyl ester (**1a**)

A freshly prepared of solution of LDA (10.2 mmol) was cooled to -78°C and a solution of ethyl acetate (0.976 ml, 10 mmol) in dry THF (4 ml) was added dropwise. After stirring for 15 minutes the pale yellow solution was treated with a solution of carbon disulphide (761 mg, 10 mmol, freshly distilled from calcium hydride) in dry THF (4 ml) which resulted in an intense red colour. The solution was allowed to warm to 0°C over 2 hours and then cooled to -78°C and treated with a freshly prepared solution of LDA (10.2 mmol) in THF (4 ml). After stirring for 30 minutes a solution of

1,3-dibromopropane (2.019 g, 1.015 ml, distilled from calcium chloride) in dry THF (5 ml) was added dropwise. The reaction mixture was then allowed to warm to room temperature over 1 hour, stirred for a further 2 hours then quenched with saturated aqueous ammonium chloride (10 ml). The product was extracted with ethyl acetate (3 x 10 ml) and the combined organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The product was isolated by column chromatography (Kieselgel 60H, 5% ethyl acetate in petrol) which gave (**1a**) as an orange/yellow oil (755mg, 37%) (Found: C, 47.8; H, 6.19. $C_8H_{12}O_2S_2$ requires C, 47.02; H, 5.92%); υ_{max} 1680, 1500 cm^{-1}; δ_H (270 MHz; $CDCl_3$), 1.25 (3H, t, J = 7 Hz), 2.19 (2H, quintet, J = 7 Hz), 2.94-3.00 (4H, 2xt, J = 6 Hz, $7^1/_2$ Hz), 4.14 (2H, q, J = 7 Hz), 6.11 (1H, s); *m/z* (70 eV E.I.) 204 (M^+, 65%), 159 (90), 132 (100), 85 (45).

2-(2-Furanylmethylene)-1,3-dithiane (**1e**)

2-Trimethylsilyl-1,3-dithiane (**0.95 ml,** 5 mmol) was dissolved in dry THF (8 ml) under nitrogen, cooled to -60°C and treated with *n*-butyl lithium (3.44 ml, 5.5 mmol) which was added dropwise. The resulting pale yellow solution was allowed to warm to room temperature over 2 hours then cooled to -78°C and treated with a solution of furfural (0.414 ml, 5.0 mmol) in dry THF (4 ml) which was added dropwise. The reaction mixture was allowed to warm to room temperature over 15 hours, quenched with saturated aqueous ammonium chloride and the product was extracted with ethyl acetate. The combined organic extracts were dried, filtered and concentrated by rotary evaporation. The product was purified by column chromatography (Kieselgel 60H, 2% ethyl acetate in petrol) to yield (**1e**) as a yellow oil (660 mg, 66%); δ_H ($CDCl_3$, 60 MHz), 1.7-2.2 (2H, m), 2.5-2.9 (4H, m), 6.25 (1H, dd, J = 2,3 Hz), 6.4 (1H, d, J = 3 Hz), 6.5 (1H, s), 7.15 (1H, d, J = 2 Hz). Lit.[102] (vinyl H) 6.7 (1H, s).

[1-(1,3-Dithian-2-ylidene)ethyl]-carbamic acid ethyl ester (4)

Ethyl chloroformate (115 mg, 1.0 mmol) and (**1c**) (146 mg, 1.0 mmol) were dissolved in cyclohexane (2 ml) and heated under reflux using an oil bath, under nitrogen. After five hours the starting material was consumed and the major product was isolated by column chromatography (Kieselgel 60H, 5% ethyl acetate in petrol) to yield (4) as a colourless liquid (12 mg, 5%). Compound (4) was also prepared as follows: To a freshly prepared solution of BDP (5 mmol) in toluene/dichloromethane (1:2, 15 ml) was added a solution of N-ethoxycarbonyl alanine methyl ester (875 mg, 5.0 mmol) in dichloromethane (10 ml) at room temperature. After stirring for 2 days at room temperature the. reaction was worked-up using the standard procedure and the product isolated by column chromatography (Kieselgel 60H, 5% ethyl acetate in petrol) to give (4) as a colour liquid (54.3 mg, 5%); (Found: m^+, 233.0507, $C_9H_{15}NO_2S_2$ requires m, 233.0542, Δ = 16.1 ppm); υ_{max} 3350, 1700, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$), 1.27 (3H, t, J = 7 Hz), 2.17 (2H, m), 2.41 (3H, s), 2.78-2.82 (4H, m), 4.13 (2H, q, J = 7Hz), 7.36 (1H, s, broad); [The ^1H n.m.r. spectrum (270 MHz, $CDCl_3$) of (4) prepared by cycloaddition showed additional peaks due to the presence of (5); 1.25 (3H, t, J = 7 Hz), 2.0 (2H, m), 2.36 (3H, s), 2.6 (2H, dddd, J = 1, 3, 6, 14 Hz), 3.2 (2H, ddd, J = 3.5, 9, 14 Hz), 4.15 (2H, q, J = 7 Hz), 4.28 (1H, s). The ratio of (4):(5) was 1.6:1. These peaks were absent from the spectrum of (4) prepared from alanine]; *m/z* (70 eV E.I.), 233 (M^+, 50%), 162 (25), 119 (100).

1,3-Dithian-2-ylidenemethyl)carbamic acid ethyl ester (7)

A solution of (**1b**) (98.4 mg, 0.745 mmol) and ethyl azidoformate (860 mg, 7.45 mmol) in cyclohexane (1 ml) was heated under reflux in an oil bath, under nitrogen. After 3 hours the starting material had been consumed and the products were separated by column chromatography to give (7) as an oil (14.6 mg, 8.9%) and (8) as an oil (67.2 mg, 29%). Compound (7) could also be prepared as follows; to a freshly

prepared solution of BDP (5 mmol) in toluene/dichloromethane (1:2, 15 ml) was added a solution of N-ethoxycarbonyl glycine ethyl ester (5 mmol) in dichloromethane (10 ml). After stirring for 2 days at room temperature, three products had formed. The reaction was ...worked-up by the normal procedure and the products were separated by column chromatography (Kieselgel 60 H, ethyl acetate in petrol). The least polar product (184.2 mg, 17%) was identical to (**7**). Data for (**7**); (Found: m^+, 219.0402, $C_8H_{13}NO_2S_2$ requires m, 219.0386, Δ = 6.4 ppm); υ_{max} 3200, 1720, 1600 cm^{-1}; δ_H (270 MHz; $CDCl_3$), 1.25 (3H, t, *J* = 7 Hz), 2.17 (2H, m), 2.75-2.8 (4H, 2xt, *J* = 3 Hz, *J* = 3 Hz), 4.17 (2H, q, *J* = 7 Hz), 6.9 (1H, d, broad, *J* = 11 Hz), 7.18 (1H, d, *J* 11 Hz), δ_H (67.8 MHz; $CDCl_3$), 14.30 (CH_3), 26.23 (CH_2), 31.20 (CH_2), 31.83 (CH_2), 61.72 (CH_2), 129.64 (CH), 153 , 194 ; *m/z* (70 eV E.I.) 219 (M^+, 100%), 146 (190), 119 (45), 73 (50)

(1,3-Dithian-2-ylidene)methylene bis (carbamic acid ethyl ester) (**8**)

For the preparation of (**8**) see (**7**). The more polar product was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to give (**8**) (67.2 mg, 29%) as an oil; υ_{max} 3300, 2950, 1700 cm^{-1}, δ_H (60 MHz; $CDCl_3$) 1.2 (6H, t, *J* = 7 Hz), 2.0-2.3 (2H, m), 2.8-2.95 (4H, m), 4.0-4.4 (4H, q, *J* = 7 Hz), 7.0-7.5 (2H, broad); *m/z* (70 eV. E.I.) 306 (M^+, 7.5%), 233 (10), 194 (100). Compound (**8**) was not characterized by elemental analysis or high resolution mass determination.

(1,3-Dithian-2-ylidene phenylmethyl)carbamic acid ethyl ester (**9**)

A solution of (**1d**) (208 mg, 1 mmol) and ethyl azidoformate (230 mg, 2 mmol) in cyclohexane (4 ml) was heated under reflux using an oil bath, under an atmosphere of nitrogen. Further additions of ethyl azidoformate were made after 3,6 and 9 hours. After 14 hours the starting material had been consumed. The product was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to yield (**9**)

as a yellow oil (98 mg, 33%). A solution of (**9**) was also prepared by treating amine (**10**) with 1.1 equivalents of ethyl chloroformate and pyridine in dichloromethane at 0°C. The product was purified by column chromatography to give (**9**) (50%) which could be recrystallized from petrol, m.p. 101.2-101.9°C (Found: C, 57.0; H, 5.84; N, 4.68. $C_{14}H_{17}NO_2S_2$ requires C, 56.9; H, 5.80; N, 4.74%); υ_{max} 3260, 1680 cm^{-1}; δ_H ($CDCl_3$, 270 MHz), 1.12 (3H, t, J = 7 Hz), 2.16 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.97 (2H, t, J = 6 Hz), 4.02 (2H, q, J = 7 Hz), 6.76 (1H, s broad), 7.30-7.35 (5H, m); δ_C (D_6-Acetone; 68 MHz), 14.76 (CH_3), 25.17 (CH_2), 30.00 (CH_2), 30.42 (CH_2), 61.21 (CH_2), 128.28 (CH), 129.48 (CH), 129.74 (CH), 148.55; *m/z* (70 eV E.I.) 295 (M^+, 100%), 249 (65), 222 (30), 175 (30), 149 (30), 119 (95), 104 (65).

[Propan-1-thioic acid, S-(3-mercaptopropyl)ester-2-yl] carbamic acid ethyl ester (**16**)

For the preparation of (**16**) see (**4**). The reaction of BDP with alanine derivative (**14**) also gave, in addition to (**4**), a more polar product which was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to give (**16**) as an oil (227 mg, 23%) υ_{max} 3300, 2980, 2560, 1700 cm^{-1}, δ_H (270 MHz; $CDCl_3$), 1.25 (3H, t, J = 7 Hz), 1.40 (1H, t, J = 8 Hz), 1.41 (3H, d, J = 7 Hz), 1.89 (2H, quintet, J = 7 Hz), 2.58 (2H, q, J = Hz), 3.00 (2H, t, J = 7 Hz), 4.13 (2H, q, J = 7 Hz), 4.4-4.5 (1H, q, broad, J = 8 Hz), 5.27 (1H, broad); *m/z* (C.I.) 252 (MH^+, 2%), 234 (1), 190 (20), 176 (60), 144 (55), 116 (100). Compound (**16**)was not characterized by elemental analysis or high resolution mass determination.

[Ethanethioic acid, S-(3-mercaptopropyl)ester-2-yl] carbamic acid ethyl ester (**20a**)

For the preparation of (**20a**) see (**7**). The reaction of BDP with glycine derivative (**18**) gave three compounds which were isolated by column chromatography. The most polar compound (**20a**) (189.4 mg, 16%) was a colourless oil. υ_{max} 3350, 2980, 2560, 1700 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25 (3H, t, J = 7 Hz), 1.38 (1H, t, J = 8

Hz), 1.87 (2H, quintet, J = 7 Hz), 2.56 (2H, dt, J = 7,8 Hz), 3.01 (2H, t, J = 7 Hz), 3.93 (2H, d, J = 5.5 Hz), 4.15 (2H, q, J = 7 Hz), 5.18 (1H, broad); *m/z* (70 eV E.I.) 219 (M^+-H_2O, 2%), 175 (5), 130 (20), 102 (100). Compound (**20a**) was not characterized by elemental analysis or high resolution mass determination.

[2-(3-Mercaptoprop-1-yl)-1,3-dithian-2-yl]methyl carbamic acid ethyl ester (**20b**)

For the preparation of (**20b**) see (**7**). The reaction of BDP with glycine derivative (**18**) gave three compounds which were isolated by column chromatography. The middle compound (**20b**) (95.0 mg, 11%) was a colourless oil; υ_{max} 3350, 2950, 2550, 1700 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.26 (3H, t, J = 7 Hz), 1.43 (1H, t, J = 8 Hz), 1.91 (2H, quintet, J = 7 Hz), 1.80-1.98 (1H, m), 2.0-2.1 (1H, m), 2.64 (2H, dt, J = 7,8 Hz), 2.73-2.83 (6H, m), 3.14 (2H, ddd, J = 2.5, 10, 13.5 Hz), 3.68 (2H, d, J = 6 Hz), 4.14 (2H, q, J = 7 Hz), 5.24 (1H, broad). δ_H (68 MHz, $CDCl_3$) 14.53 (CH_3), 23.61 (CH_2), 24.26 (CH_2), 27.28 (CH_2), 30.65 (CH_2), 33.05 (CH_2), 49.56 (CH_2), 61.11 (CH_2), 62.69, 157; *m/z* (70 eV E.I.) 220 (M^+-S $(CH_2)_3SH$, 95%), 219 (30), 174 (20), 146 (25), 132 (25), 119 (100). Compound (**20b**) was not characterized by elemental analysis or high resolution mass dtermination.

4-Methyl-N-(3-methyl-1,4-dithiepan-2-ylidene)-benzene sulphonamide (**22**)

A solution of (**1c**) (146 mg, 1.0 mmol) and tosyl azide (**21**) (197 mg, 1 mmol) in cyclohexane (3 ml) was heated under reflux in an oil bath, under nitrogen. After 5 hours the major product was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to yield (**22**) (146 mg, 46%). When a catalytic amount of calcium carbonate was included in the reaction mixture the starting material was absent after 3 hours at reflux and the product (**22**) was isolated in 89% yield. Recrystallization from methanol gave colourless crystals, m.p. 145.0 - 146.0^{0}C (Found: C, 49.3; H, 5.48; N, 4.29. $C_{13}H_{17}NO_2S_3$ requires C, 49.50; H, 5.43; N, 4.44%); υ_{max} 1600, 1380, 1150

cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.40 (3H, d, J = 7 Hz), 2.0-2.15 (1H, dddd, J = 2.5, 8, 14, 26 Hz), 2.43 (3H, s), 2.5-2.6 (1H, m), 2.9-2.95 (2H, m), 3.05-3.10 (1H, ddd, J = 2, 5, 15 Hz), 3.3-3.4 (1H, ddd, J = 2, 11, 15 Hz), 4.03 (1H, q, J = 7 Hz), 7.30 (2H, d, J = 7.9 Hz, part of AA'BB'), 7.85 (2H, d, J = 8.2 Hz, part of AA'BB'); δ_C (68 MHz; $CDCl_3$), 18.88 (CH_3), 21.47 (CH_3), 31.17 (CH_2), 32.24 (CH_2), 33.31 (CH_2), 46.45 (CH), 127.15 (CH), 129.19 (CH), 137.52, 143.49, 186.44; *m/z* (70 eV E.I.), 315 (M^+, 15), 155 (40), 133 (40), 106 (90), 91 (100).

Crystal data:(compound 22) [$C_{13}H_{17}NO_2S_3$], M = 315.48, Monoclinic, space group $P2_1/c$, a = 12.651(3), b = 6.363(2), c = 20.000(4) Å, = 106.86(2)°, U = 1540.8 $Å^3$, F(000) = 664, μ(Mo-K_α) = 4.22 cm^{-1}, Z = 4, Dc = 1.360 g cm^{-3}

Data were collected on a Philips PW1100 diffractometer with a constant scan width of 0.80° in the 0-range 3-23° using graphite crystal monochromated Mo-K_α radiation with a crystal of dimentsions 0.32 x 0.22 x 0.16mm. A total of 2431 reflections were recorded, with a 0.20 scan mode. No signficiant change occurred in three reference reflections which were monitored every 5h. Lorenz polarisation corrections were applied to the data and equivalent reflections were merged to give a total of 1458 unique reflections with $I/\sigma(I) > 2.0$.

The space group was unambiguously determined as $P2_1/c$ from the systematic absences in the data: OkO, k = 2n + 1 and hO1, l = 2n + 1. The 'automatic' centrosymmetric direct methods procedure of the SHELX program failed to yield a solution. A convergence map was calculated using reflections with E-values in the range 1.3 to 3.0. From this the origin was fixed using three reflections -1 2 8, 5 5 8 and 2 6 3, and the remaining 'path breaks' (3 1 18 and 10 4 4) were entered as multisolutions. The first tangent-map calculated in order of decreasing figure of merit revealed the positions of most of the non-hydrogen atoms apart from C(5), C(6) and C(7) which were found in a subsequent difference-Fourier map. Later a difference-Fourier synthesis calculated using only reflections with sin0 < 0.35 revealed

positions for all the H-atoms. For consistency the H-atoms were included at calculated positions 9C-H 1.08 Å) assuming idealised sp^3 or sp^2 hybridisation as appropriate, the 'best' H-atom located for each methyl group being used to define the orientation of the CH_3 groups. The H-atom thermal parameters were tied to free variables resulting in final thermal parameters of 0.07 (sp^2), 0.10 (sp^3) and 0.16 (methyl) $Å^2$. In the final stages of full-matrix refinement all the non hydrogen atoms were assigned anisotropic thermal parameters. Weights were applied to the individual reflections as $1/\sigma^2(F)$ and refinement converged at R 0.0470 and Rw 0.0459, with 176 parameters. Neutral scattering factors, corrected for the real and imaginary parts of the anomalous scattering, were used for all atoms and were taken from International Tables for X-ray Crystallography Volume 4.

4-Methyl-N-(1,4-Dithiepan-2-ylidene)-benzene sulphonamide (23)

A solution of (**1b**) (118.4 mg, 0.90 mmol) and tosyl azide (256.3 mg, 1.08 mmol) in cyclohexane (2 ml) was heated in an oil bath under reflux, under nitrogen. After 2 hours the starting material had been consumed and the product crystallized from the reaction mixture as a colourless solid which was isolated by filtration followed by washing with petrol. This gave (**23**) (160 mg, 59%) which could be recrystallized from methanol, m/p. 153.7-154.7°C (Found :C, 47.5; H, 5.01; N, 4.64; $C_{11}H_{15}NO_2S_3$ requires C, 47.81; H, 5.02; N, 4.65%); υ_{max} 1600, 1300, 1150 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.43 (5H, broad), 2.85 (2H, broad), 3.16 (2H, broad), 3.70 (2H, broad), 7.31 (2H, d, J = 7.9 Hz, part of AA'BB'), 7.86 (2H, d, J = 8.2 Hz, part of AA'BB'); δ_C (68 MHz; $CDCl_3$) 21.57 (CH_3), 32.50 (CH_2), 32.99 (CH_2), 34.05 (CH_2), 42.55 (CH_2), 127.47 (CH), 129.38 (CH), 143.92; *m/z* (70 eV E.I.) 301 (M^+, 35%), 155 (25), 146 (35), 119 (30), 106 (90), 91 (100).

4-Methyl-N-(3-phenyl-1,4-dithiepan-2-ylidene)-benzene sulphonamide (24)

A solution of (**1d**) (416 mg, 2 mmol) and tosyl azide (394 mg, 2 mmol) in cyclohexane (2 ml) was heated in an oil bath under reflux, under nitrogen. After 9 hours, 2 products had formed and were isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol). The less polar compound (**24**) (180 mg, 24%) was recrystallized from methanol to give a pale yellow crystalline cold, m.p. 164.0-164.8°C (Found: C, 57.1; H, 5.06; N, 3.71; $C_{18}H_{19}NO_2S_3$ requires C, 57.3; H, 5.0; N, 3.7%); υ_{max} 1600, 1300, 1140, 1080, 1040 cm^{-1}; δ_H (270 MHz, $CHCl_3$) 2.15-2.35 (2H, m), 2.40 (3H, s), 2.80-2.90 (1H, ddd, J = 3.5, 7, 15 Hz), 2.95-3.05 (2H, m), 3.15-3.25 (1H, m), 5.16 (1H, s, broad), 7.23 (2H, d, J = 8.2 Hz, part of AA'BB'), 7.71 (2H, d, J =8.2 Hz), 7.30-7.35 (5H, m); δ_C (68 MHz, $CDCl_3$) 21.54 (CH_3), 31.17 (CH_2), 32.60 (CH_2), 57.51 (CH), 127.11 (CH), 127.92 (CH), 128.31 (CH), 128.57 (CH), 129.19 (CH), 135.35, 137.75, 143.49; *m/z* (C.I.) 378 (MH^+, 1%), 279 (1), 272 (1), 222 (2), 212 (2), 172 (100), 15 (20).

1,1-Dihydro-1-[[(4-methylpheyl)sulphonyl]imino]-2-(phenylmethylene)-1,3-dithiane (25)

For the preparation of (**25**), see compound (**24**). The more polar compound (**25**) (135 mg, 18%) was recrystallized from methanol to give a colourless crystalline solid. Compound (**25**) was also prepared from (**1d**) as follows; a solution of (**1d**) (104 mg, 0.5 mmol) in dichloromethane (2 ml) was cooled to 0°C and treated with a solution of chloramine-T (282 mg, 1 mmol) in methanol. After stirring for 1 hour (**1d**) was absent and water (2 ml) was added. The product was extracted with ethyl acetate, the combined organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The product was then isolated by column chromatography (Kieselgel 60H, 50% ethyl acetate in petrol) and recrystallized from methanol to give (**25**) (42 mg, 22%) as a colourless crystalline solid. m.p.

155.3-156.3°C (Found: C, 57.1; H, 5.00; N, 3.65; $C_{18}H_{19}NO_2S_3$ requires C, 57.3; H, 5.0; N, 3.7%); υ_{max} 1600, 1260, 930 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 2.33 (3H, s), 2.45-2.55 (1H, m), 2.62-2.68 (1H, m), 2.70-2.74 (1H, m), 2.80-2.90 (1H, m), 3.17-3.37 (2H, m), 7.25 (2H, d, *J* = 7.9 Hz, part of AA'BB'), (4H, AA'BB'), 7.36 (3H, m), 7.52-7.56 (2H, m), 7.82 (2H, d, *J* = 8.1 Hz, part of AA'BB'); δ_C (68 MHz, $CDCl_3$), 21.28 (CH_3), 26.34 (CH_2), 31.04 (CH_2), 51.47 (CH_2), 126.24 (CH), 127, 128.38 (CH), 129.29 (CH), 129.93 (CH), 130.29 (CH), 132.65, 139.41 (CH), 141.81; *m/z* (C.I.) 378 (MH^+, 10%), 209 (40), 208 (45), 172 (100), 155 925), 134 (20)

2-(2-Furanylmethylene)-1,1-dihydro-1-[[(4-methylphenyl)sulphonyl]imino]-1,3-dithiane (26)

A solution of (**1e**) (198 mg, 1 mmol) and tosyl azide (220 mg, 1.2 mmol) in cyclohexane (2 ml) was heated under reflux in an oil bath, under nitrogen. After 19 hours (**1e**) was absent and the major product was isolated by column chromatography to give (**26**) (121 mg, 33%) which was recrystallized from methanol to give a crystalline solid. Compound (**26**) was also prepared by dissolving (**1e**) (25.9 mg, 0.13 mmol) in dichloromethane (1 ml), cooling to 0°C and adding a solution of chloramine-T (73 mg, 0.26 mmol) in methanol (1 ml). After 15 minutes (**1e**) was absent and the reaction mixture was filtered then the solvent was removed by rotary evaporation. Compound (**26**) (12.2 mg, 26%) was obtained by recrystallisation from the crude reaction mixture using methanol. m.p. 171.1-171.6°C (Found: C, 52.25; H, 4.70; N, 3.64; $C_{16}H_{17}NO_3S_3$ requires C, 52.29; H, 4.66; N, 3.81%); δ_H (270 MHz, $CDCl_3$) 2.35 (3H, s), 2.45-2.55 (1H, m), 2.65-2.75 (2H, m), 2.83-2.93 (1H, m), 3.12-3.33 (2H, m), 6.49 (1H, dd, *J* = 1.8, 3.5 Hz), 6.91 (1H, d, J = 3.5 Hz), 7.21 (2H, d, *J* = 7.8 Hz, part of AA'BB'), 7.29 (1H, s), 7.51 (1H, dd, *J* = 0.5, 1.8 Hz), 7.80 (2H, d, *J* = 8.4 Hz, part of AA'BB'); δ_C (68 MHz; $CDCl_3$) 21.28 (CH_3), 25.53 (CH_2), 30.52 (CH_2), 50.92 (CH_2), 112.19 (CH), 116.34 (CH), 123.51, 126.17 (CH), 126.69 (CH), 129.22 (CH), 141.35, 141.81, 144.40 (CH), 148.97; *m/z* (low eV E.I.) 367 (M^+, 20),

243 (20), 212 (25), 198 (100).

2-(4-Azidobutylidene)-1,3-dithiane (34)

To a freshly prepared solution of BDP (6 mmol) in dichloromethane/toluene (2:1, 18 ml) was added a solution of (**43**) (940 mg, 6.0 mmol) in dichloromethane (12 ml). After stirring for 3 days at room temperature the reaction was worked-up using the normal procedure and the product was isolated by column chromatography to give (**34**) (790 mg, 61.4%) as a pale yellow oil. (Found: C, 45.0, H, 6.31; N, 18.7; $C_8H_{13}N_3S_2$ requires C, 44.62; H, 6.08, N, 19.51); (Found: m^+-N_2; 187.0487, $C_8H_{13}NS_2$ requires 187.0489, Δ = -1.5 ppm).; υ_{max} 2900, 2070, 1570, 1430 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.68 (2H, quintet, J = 7 Hz), 2.16 (2H, m), 2.31 (2H, q, J = 7 Hz), 2.87 (4H, m), 3.29 (2H, t, J = 7 Hz), 5.90 (1H, t, J = 7.5 Hz); *m/z* (70 eV E.I.) 187 (M^+-N_2, 25%), 159 (15), 145 (40), 119 (100), 106 (40).

2-(4-Bromobutylidene)-1,3-Dithiane (37)

A freshly prepared solution of BDP (1 mmol) in toluene/dichloromethane (1:2, 3 ml) was treated with a solution of (**36**) (195 mg, 1 mmol) in dichloromethane (2 ml) and stirred for 3 days at room temperature. The reaction was worked-up using the normal procedure and the product was purified by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to give (**37**) (141.5 mg, 56%) as an oil; δ_H (60 MHz; $CDCl_3$) 5.5 (1H, t, J = 7 Hz), 1.5-3.5 (remaining protons, m); m/z (C.I.) 255 (MH^+, 50 %), 253 (MH^+, 50%), 204 (40), 181 (20), 173 (25), 165 (95), 163 (100). Compound (**37**) was not stable and decomposed to give a complex mixture of products.

2-($\Delta^{1,2}$-Pyrrolidin-2-yl)-1,3-dithiane (38)

In a typical reaction, a freshly prepared sample of (**34**) was placed in a dried

flask and *n*-octane (2 ml per mmol of (**34**) was added. The solution was heated under reflux using an oil bath at 150°C, under an atmosphere of nitrogen. After 4 hours at reflux, (**34**) was absent and (**38**) had formed cleanly (visualization : P.M.A.). The solution of (**38**) in *n*-octane was stable for several hours if air and moisture were excluded, but all attempts to isolate (**38**) were unsuccessful and resulted in the formation of a number of more polar products.

5-Azidopentanoic acid methyl ester (**43**)

A solution of 5-bromopentanoic acid (1.81 g, 10 mmol) in dry methanol (10 ml) was cooled in an ice bath and treated with thionyl chloride (2.0 ml, 25 mmol) which was added dropwise by syringe. After warming to room tempearture and stirring for 6 hours the solution was concentrated by rotary evaporation, treated with 5% aqueous potassium carbonate (10 ml) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with distilled water (10 ml), dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation to give (**36**); υ_{max} 3000, 1750, 1450 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.8 (4H, m), 2.4 (2H, t, J = 7 Hz), 3.5 (2H, t, J = 7 Hz), 3.7 (3H, s); *m/z* 197 (MH^+, 100%), 195 (MH^+, 95%), 165 (5), 115 (70).

Compound (**36**) was dissolved in DMF (10 ml) and treated with sodium azide (780 mg, 12 mmol) and potassium iodide (10 mg) then stirred for 18 hours. Water (20 ml) was added and the product extracted into petrol (3 x 25 ml). The combined organic layers were washed with water (10 ml) then dried over sodium sulphate, filtered and the solvent was removed by rotary evaporation to yield (**43**) (1.34 g ,85 % overall yield) as a colourless liquid. υ_{max} 2950, 2080, 1730, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.55-1.76 (4H, m), 2.34 (2H, t, J = 7 Hz), 3.28 (2H, t, J = 6.5 Hz), 3.66 (3H, s); *m/z* (C.I.) 158 (MH^+, 20%), 130 (35), 115 (40, 98 (100). Azide (**36**) was not characterized by elemental analysis or high resolution mass determination.

2-[Pyrrolidine-1-(carboxylic acid phenylmethyl ester)-2-ylidene]-1,3-dithiane (**52**)

A solution of (**34**) (435.9 mg, 2.02 mmol) in *n*-octane (4 ml) was heated in an oil bath under reflux for 4 hours, under an atmosphere of nitrogen. The resulting solution of (**38**) was allowed to cool, diluted with dichloromethane (4 ml) and then cooled to 0°C using an ice bath. Pyridine (316 mg, 4.0 mmol) was added, followed by benzyl chloroformate(344 mg, 2.0 mmol). After stirring for 3 hours with 2 subsequent additions of benzyl chloroformate, the solvent was removed and the reaction mixture was purified by column chromatography (Kieselgel 60H, 10-15% ethyl acetate in petrol) which gave (**52**)(421.1 mg, 64.9%) as a colourless liquid.

Compound (**52**) could also be prepared as follows: a solution of freshly prepared BDP (4 mmol) in dichloromethane/toluene (2:1, 12 ml) was treated with a solution of proline derivative (**55**) (1.40 g, 4 mmol) in dichloromethane (8 ml). After stirring for 5 days at room temperature the normal work-up procedure was followed and the product was purified by column chromatography (flash silica, 10-25% ethyl acetate in petrol) to yield (**52**) (450.4 mg, 35%) as an oil; (Found: m^+, 321.0855, $C_{16}H_{19}NO_2S_2$ requires m, 321.0855); υ_{max} 3000, 2900, 1680, 1600 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85 (2H, quintet, J = 7.5 Hz), 2.10 (2H, m), 2.66 (2H, t, J = 7.5 Hz), 2.71 (2H, t, J = 5.5 Hz), 2.80 (2H, t, J = 5.5 Hz), 3.66 (2H, t, J = 7.5 Hz), 5.16 (2H, s), 7.26-7.38 (5H, m); δ_C (68MHz; $CDCl_3$) 21.18 (CH_2), 24.94 (CH_2), 30.52 (CH_2), 30.59 (CH_2), 30.78 (CH_2), 48.88 (CH_2), 67.17 (CH_2), 108, 127.72 (CH), 127.86 (CH), 128.09 (CH), 136.00, 140.15, 152.77; *m/z* (70 eV E.I.) 321 (M^+, 10%), 186 (25), 120 (20), 105 (55), 91 (100)..

N-(Phenylmethyloxycarbonyl)proline methyl ester (**55**)

A solution of (**52**) (111.0 mg, 0.34 mmol) in a mixture of acetic acid (2 ml)

and concentrated hydrochloric acid (4 drops) was heated under reflux for 5 minutes. The product (**56**) was extracted with petrol (4 x 5 ml) and the combined organic layers were dried with anhydrous sodium sulphate, filtered and then concentrated by rotary evaporation. The crude residue was dissolved in dry methanol (2 ml) and treated with a freshly prepared solution of sodium methoxide (excess) in methanol at room temperature. After 30 minutes (**56**) was absent from the reaction mixture (T.L.C.) Water (2 ml) was added and the product was extracted with ethyl acetate (3 x 5 ml). The extracts were dried, filtered and concentrated and the product was isolated by column chromatography (Kieselgel 60H, 10-15% ethyl acetate in petrol) to yield (**55**) (77.6 mg, 84%) as a colourless oil.

A sample of (**55**) was also prepared by treating N-(phenylmethyloxycarbonyl) proline with thionyl chloride in methanol using the procedure described in the preparation of (**36**); υ_{max} 2950, 2850, 1730, 1680, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.75-1.95 (3H, m), 2.05-2.24 (1H, m), 3.35-3.60 (2H, m), 3.50 and 3.65 (3H, 2 x s), 4.24-4.35 (1H, 2 x dd, J = 5, 9 Hz), 4.94-5.14 (2H, 2 x AB), 7.24-7.29 (5H, m); *m/z* (70 eV E.I.) 263 (M^+, 5%), 206 (25), 160 (25), 91 (100). Spectroscopic data are in agreement with those reported previously[221].

Pyrrolidine-2-carbothioic acid S-(3-mercaptopropyl ester)-1-carboxylic acid phenylmethyl ester (**56**)

A solution of (**52**) (188.6 mg, 0.587 mmol) in a mixture of glacial acetic acid (2 ml) and concentrated hydrochloric acid (4 drops) was heated under reflux for 5 minutes. The product was extracted with water (5 ml) and ethyl acetate (3 x 10 ml) and the combined organic extracts were dried with anhydrous sodium sulphate, filtered and then concentrated by rotary evaporation. The product was isolated by column chromatography to give (**56**) (114.1 mg, 58%) as a colourless liquid. υ_{max} 2950, 2500, 1680, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.34, 1.39 (1H, 2 x t, J = 8 Hz), 1.77-1.89 (2H,

2 x quintet, $J = 7$ Hz), 1.90-2.20 (4H, m), 2.47-2.57 (2H, 2 x q, $J = 8$ Hz), 2.91-2.98 (2H, 2 x t, $J = 7$ Hz), 3.45-3.70 (2H, m), 4.45, 4.55 (1H, 2 x dd, $J = 3, 8$ Hz), 5.05-5.2 (2H, AB and s), 7.27-7.36 (5H, m); *m/z* (C.I.) 340 (MH^+, 6%), 322 (1), 296 (35), 232 (5), 204 (55), 160 (30), 91 (100). Compound (**56**) was not characterized by elemental analysis or high resolution mass determination.

[4-(1,3-Dithian-2-yl)-4-oxobutan]-1-yl carbamic acid phenylmethyl ester (**57**)

Compound (**52**) (473.0 mg, 1.47 mmol) and dissolved in a mixture of acetic acid (2 ml), water (2 ml) and concentrated hydrochloric acid (4 drops) and the solution was heated under reflux for 1 hour. The products were extracted (5 ml water, 3 x 10 ml ethyl acetate) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered then concentrated by rotary evaporation. Purification by column chromatography (Kieselgel 60H, 10-25% ethyl acetate in petrol) gave (**56**) (238.9 mg, 48%) followed by (**57**) (40.8 mg, 8.2%) as a colourless oil. υ_{max} 3350, 2950, 1680, 1500 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.84 (2H, quintet, $J = 7$ Hz), 1.97-2.07 (2H, m), 2.5 (2H, ddd, $J = 3, 5.5, 14$ Hz), 2.69 (2H, t, $J = 7$ Hz), 3.14-3.25 (4H, m), 4.19 (1H, s), 4.95 (1H, broad), 5.09 (2H, s), 7.26-7.34 (5H, m); *m/z* (C.I.) 340 (MH^+, 25%), 322 (5), 296 (25), 248 (10), 222 (10), 204 (45), 160 925), 119 930), 91 (100). Compound (**57**) was not characterized by elemental analysis or high resolution mass determination.

2-(Pyrrolidin-2-yl)-1,3-dithiane (**58**)

A solution of (**34**) (444 mg, 2.07 mmol) in *n*-octane (10 ml) was heated under reflux in an atmosphere of nitrogen for 4 hours to generate (**38**). After cooling to room temperature, the reaction mixture was diluted with an equal volume of dry methanol, cooled to 0°C and treated with sodium borohydride (160 mg, 4 mmol). The reaction mixture was stirred for 1 hour after which time (**38**) was absent. Water was added and the product was extracted with ether (3 x 25 ml). The combined extracts

were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The product was isolated by column chromatography (Kieselgel 60H, 0-60% methanol in ethyl acetate) to give (**58**) (329.0 mg, 1.74 mmol, 84.3%) as a waxy solid which became crystalline on standing, m.p. 27-29°C (Found: C, 50.76; H, 8.10; N, 7.2; $C_8H_{15}NS_2$ requires C, 50.75; H, 7.99; N, 7.40%); υ_{max} 3200 (broad), 2900, 1450 cm^{-1}, δ_H (270 MHz; $CDCl_3$) 1.73-2.14 (6H, m), 2.77-3.17 (6H, m), 3.53 (1H, q, J = 7.5 Hz), 4.11 (1H, d, J = 8 Hz), 4.32 (1H, broad); δ_C (68 MHz; $CDCl_3$) 25.20 (CH_2), 25.66 (CH_2), 29.09 (CH_2), 29.158 (CH_2), 29.29 (CH_2), 46.34 (CH_2), 52.80 (CH), 60.85 (CH). *m/z* (C.I.) 190 (MH^+, 100%); (70 eV E.I.) 119 (5), 70 (100).

2-[1-(4-Methylphenylsulphonyl)pyrrolidin-2-yl]-1,3-dithiane (**58a**)

A solution of (**58**) (226.0 mg, 1.196 mmol) was dissolved in dichloromethane (5 ml) cooled to 0°C and treated with tosyl chloride (251 mg, 1.32 mmol), pyridine (0.5 ml) and DMAP (5 mg). The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The solvent was removed by rotary evaporation and the product was isolated by column chromatography (flash silica, 10-20% ethyl acetate in petrol) to give (**58a**) (325.2 mg, 79.3%) as a solid which was recrystallized from methanol, m.p. 134.7-135.7°C; (Found: C, 52.4; H, 6.23; N, 4.05; $C_{15}H_{21}NO_2S_3$ requires C, 52.44; H, 6.18; N, 4.07%); υ_{max} 2930, 1600, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.39-1.51 (1H, m), 1.62-1.76 (1H, m), 1.82-1.97 (2H, m), 2.06-2.17 (2H, m), 2.43 (3H, s), 2.83-3.03 (4H, m), 3.24 (1H, dt, J = 6.9, 10.4 Hz), 3.39 (1H, dt, J = 6.9, 10.4 Hz), 3.88 (1H, dt, J = 4.3, 8.7 Hz), 4.75 (1H, d, J = 4.0 Hz), 4.75 (1H, d, J = 4.0 Hz), 7.32(2H, d, J=8.1Hz, part of AA'BB'), 7.76(2H, d, J=8.1Hz,part of AA'BB'); *m/z* (C.I.) 344 (MH^+, 30%), 238 (24), 224 (100), 155 (26), 147 (12),119 (17).

2-[Pyrrolidine-1-(carboxylic acid-2,2-dimethylethyl ester)-2-yl]-1,3-dithiane (**58b**)

A solution of (**58**) (183 mg, 0.97 mmol) in dichloromethane (10 ml) at room

temperature was treated with di-*tert*-butyldicarbonate (262 mg, 1.2 mmol) and stirred for 12 hours at room temperature then the solvent was removed by rotary evaporation and the residue was purified by column chromatography (flash silica, 10-20% ethyl acetate in petrol) to give (**58b**) (290 mg, 100%) as a colourless, crystalline solid, m.p. 60.6-61.6°C; (Found: C, 53.8; H, 8.08; 4.63; $C_{13}H_{23}NO_2S_2$ requires C, 53.94; H, 8.01; N, 4.84%); υ_{max} 2900, 1660, 1450, 1380 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.47 (9H, 2 x s), 1.71-1.89 (2H, m), 1.92-1.24 (2H, m), 2.06-2.20 (2H, m), 2.75-2.97 (4H, m), 3.30 (1H, dt, J = 7, 12.9 Hz), 3.38-3.57 (1H, m, broad), 4.0-4.17 (1H, broad), 4.65 (0.4H, d, J = 5 Hz), 4.84 (0.6H, d, J = 5 Hz); *m/z* (low eV E.I.) 289 (M^+, 10%), 170 (100), 114 (40), 50 (10).

2-(2-Deuteropyrrolidin-2-yl)-1,3-dithiane (**59**)

A solution of (**34**) (261.4 mg, 1.22 mmol) in octane (2 ml) was heated under reflux in an atmosphere of nitrogen for 4 hours, cooled to 0°C, diluted with dry methanol (2 ml) and then treated with sodium borodeuteride (235 mg, 4.86 mmol). The reaction was stirred at room temperature for 18 hours then water (15 ml) was added and the product was extracted with ether (3 x 10 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation. The residue was purified by column chromatography (0-45% methanol in ethyl acetate) to give (**59**) (20 mg, 8.8%) as a yellow oil; υ_{max} 3300, 2950, 2080 (weak), 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.74-2.13 (6H, m), 2.79-3.07 (6H, m), 4.06 (1H, s); *m/z* (C.I.) 191 (MH^+, 25%), 71 (100), (70 eV E.I.) 119 (2%), 71 (100). Both ^1H n.m.r. and mass spectra indicate quantitative incorporation of deuterium at the pyrrolidine C-2.

2-(4-Azido-1-deuterobutan-1-ylidene)-1,3-dithiane (**60**)

A solution of (**60a**) (1.44 g, 8.44 mmol) in dichloromethane (15 ml) was added to a freshly prepared solution of BDP (8.5 mmol) in dichloromethane/toluene

(2:1, 25 ml) then stirred at room temperature for 4 days. The normal work-up procedure was followed and the product was isolated by chromatography which gave (**60**) (1.08 g, 59.4 %) containing 25% deuterium at C-2 as judged by ^{1}H n.m.r.; δ_H (270 MHz; $CDCl_3$) 1.60-1.75 (4H, m), 2.25-2.45 (2H, m), 2.55-2.70 (2H, m), 2.87 (4H, t, J = 6 Hz), 3.29 (2H, t, J = 6.9 Hz), 5.90 (0.75H, t, J = 7.4 Hz).

5-Azido-2-deuteropentanoic acid ethyl ester (**60a**)

A solution of (**43**) (1.57 g, 10 mmol) in D-ethanol (C_2H_5OD) (5 ml) was treated with sodium ethoxide in D-ethanol at 0°C then stirred at room temperature for 18 hours. Deuterium oxide (5 ml) was added and the product was extracted with petrol (3 x 10 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation to give (**60a**) (1.443 g, 8.44 mmol) which contained 20% deuterium at C-2 as judged by ^{1}H NMR; υ_{max} 2930, 2080, 1750, 1450 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.3 (3H, t, J = 7 Hz, 1.6 (4H, m), 2.4 (1.6H, m), 3.3 (2H, m), 4.0 (2H, q, J = 7
Hz).

2-Deutero-2-(pyrrolidin-2-yl)-1,3-dithiane (**61**)

A solution of (**60**) (215 mg, 1 mmol, containing 25% deuterium at C-2) in octane (2 ml) was heated under reflux for 4 hours then cooled in ice and diluted with methanol. Sodium borohydride (76 mg, 2 mmol) was added and the reaction mixture was stirred for 30 minutes at 0°C. The product was isolated as described in the preparation of (**58**) to give (**61**)a (62.3 mg, 30.1%) which contained 8% deuterium at the dithiane C-2, as judged by ^{1}H n.m.r.; δ_H (270 MHz; $CDCl_3$) as for (**58**) except; 4.05 (0.92H, d, J = 7.3 Hz).

2-[1,3-Dithian-2-ylidene)methyl]-2-(2-azidoethyl)-1,3-dithiane (63)

The alcohol (**66**) was prepared according to the known procedure[134]. A solution of (**66**) (230 mg, 0.78 mmol) in dry THF (10 ml) was cooled to 0°C under an atmosphere of nitrogen then treated with triphenyl phosphine (204 mg, 0.78 mmol), diethylazodicarboxylate (136mg, 0.78 mmol) and diphenylphosphoryl azide (215 mg, 0.78 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for a further 18 hours. The solvent was removed by rotary evaporation and the product was isolated by column chromatography (flash silica, 2-10% ethyl acetate in petrol) to give (**63**) (156.6 mg, 63%) as a colourless oil. (Found: m^+, 263.0019; $C_{10}H_{15}S_4$ requires m, 263.0054, Δ = -14.4 ppm). υ_{max} 2900, 2070, 1550, 1420 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85-2.08 (2H, m), 2.13 (2H, quintet, J = 6.6 Hz), 2.58 (2H, t, J = 7.7 Hz), 2.77-3.04 (4H, m), 3.47 (2H, t, J = 7.7 Hz), 6.13 (1H, s); *m/z* (70 eV E.I.) 319 (M^+, 1%), 291 (5) M^+-CH_2N_3, 263 (20), 249 (10), 198 (20), 159 (100); (Found: 263.0019; $C_{10}H_{15}S_4$ requires 263.0054, Δ = -14.4 ppm).

2-Aza-1-(1,3-dithian-2-yl)-6,10-dithiaspiro[4.5]dec-1-ene (67)

A solution of (**63**) (150 mg, 0.47 mmol) in octane was heated under reflux for 4 hours in an atmosphere of nitrogen, which led cleanly to a more polar compound. The product crystallised on addition of petrol and was recrystallized from dichloromethane/ether/petrol to give (**67**) as a colourless, crystalline solid, m.p. 122.6-123.6°C; (Found: C, 45.0; H, 5.97; N, 4.74; $C_{11}H_{17}NS_4$ requires C, 45.32; H, 5.88; N, 4.81%); $_{max}$ 2900, 1630, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.95-2.18 (4H, m), 2.74 (2H, t, J = 6.4 Hz), 2.82-2.92 (4H, m), 3.05 (1H, ddd, J = 3.0, 11.9, 14.6 Hz), 3.23 (1H, ddd, J = 3.8, 6.8, 14.4 Hz), 4.04 (2H, t, J = 6.6 Hz), 4.99 (1H, s,); *m/z* (70 eV E.I.) 291 (M^+, 20%), 258 (25), 216 (20), 185 (100), 172 (25), 153 (30), 146 (70).

Crystal data: $C_{11}H_{17}NS_4$, M = 291.36, orthorhombic, a = 13.480(3), b =

13.343(2), c = 15.496(5)Å, U = 2786.9, space group Pcab, Z = 4, D_c = 1.39 gcm^{-3}, μ(Mo-K_α) = 0.64 cm^{-1}, F(000) = 1232. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24°$. The crystal was a strong diffractor and of the 2420 reflections which were collected, 1695 were unique with $I \geq 3\sigma I$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by conventional Patterson methods and refined using the SHELX suite of programs. In the final least squares cycles all atoms wer allowed to vibrate anisotropically, all others istropically. Hydrogen atoms were included at calculated positions. The final residual after 9 cycles of full-matrix least squares refinement was R = 0.0650 for unit weights. The number of parameters varied was 145. Max. final shift/esd was 0.005, the average being 0.002. The max. and min. residual densities were 0.19 and -0.22 $eÅ^{-3}$ respectively.

2-[1-(2,2-Dimethylpropanoyl)pyrrolidin-2-ylidene]-1,3-dith iane (**71**)

A solution of (**34**) (3.20g, 14.9 mmol) was dissolved in octane (20 ml) and heated under reflux in an atmosphere of nitrogen for 4 hours, then cooled to 0°C and diluted with dichloromethane (20 ml). Pyridine (1.45 ml, 18 mmol), 2,2-dimethylpropanoyl chloride (2.04 ml, 1.65 mmol) and DMAP (10 mg) were added and the reaction mixture was stirred at 0°C for 2 hours then at room temperature for 1 hour. Pyridine hydrochloride was removed by filtration, the solvent was removed by rotary evaporation and the product was isolated by column chromatography (flash silica, 15-30% ethyl acetate in petrol) to give (**71**) (2.16g, 53.7%) as a colourless oil which crystallized on standing, m.p. 100.1-101.1°C.

A sample of (**71**) was also prepared by adding a solution of N-(2,2-dimethylpropanoyl) proline methyl ester (2,13 g, 10 mmol) in dichloromethane (20 ml) to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml). The reaction mixture was stirred at room temperature for 7 days and, following the normal work-up, the product was isolated by column chromatography

(Kieselgel 60H, ethyl acetate in petrol) to give (**71**) (1.07 g, 39%) which crystallized on standing, m.p. 101.1-102.1°C (Found: C, 57.6; H, 7.92; N, 5.13; $C_{13}H_{21}NOS_2$ requires C, 57.5; H, 7.80; N, 5.16%); υ_{max} 2900, 2840, 1640, 1580, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 1.89-1.97 (1H, m), 2.12-2.14 (1H, m), 2.65 (2H, t, J = 7.6 Hz), 2.77 (2H, t, J = 5.9 Hz), 2.86 (2H, t, J = 6.1 Hz), 3.80 (2H, t, J = 7.0 Hz); *m/z* (low eV E.I.) 271 (M^+, 75%) 186 (100).

N-(2,2-Dimethylpropanoyl)pyrrolidine-2-carbothioic acid-S-(3-mercaptopropan-1-yl)ester (**72**)

A solution of N-(2,2-dimethylpropanoyl)proline methyl ester (2.13 g, 10 mmol) in dichloromethane (20 ml) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml) and stirred at room temperature for 3 days. Following the normal work-up procedure the two products were isolated by column chromatography (flash silica, 12-28% ethyl aceate in petrol) to give (**71**) (509 mg, 18.8%) and (**72**) (595 mg, 20.6%) as a colourless oil. A sample of (**72**) was also prepared by treating a solution of (**71**) (192 mg, 0.71 mmol) in dichloromethane (10 ml) at -30°C under nitrogen with boron trifluoride etherate (1.0 g, 7.1 mmol) followed by ethyl acetate (123 mg, 1.4 mmol). Stirring for 3 hours, followed by noraml work-up and chromatography, gave (**71**) (147 mg, 72%); (Found: m^+, 290.1248, $C_{13}H_{24}NO_2S_2$ requires m, 290.1248, Δ = 0.0 ppm); υ_{max} 3000, 2570, 1700, 1640 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (9H, s), 1.40 (1H, t, J = 8.1 Hz), 1.87 (2H, quintet, J = 7.1 Hz), 1.85-1.99 (2H, m), 2.01-2.17 (2H, m), 2.56 (2H, dt, J = 7.8 Hz), 2.98 (2H, t, J = 7 Hz), 3.70-3.85 (2H, m), 4.71 (1H, dd, J = 3.5, Hz); *m/z* (C.I.) 290 (MH^+, 5%), 271 (3), 257 (2), 182 (60), 154 (100) (Found: 290.1248, $C_{13}H_{24}NO_2S_2$ Δ = 0.0 ppm).

2-[1-(2,2,2-Trifluoroacetyl)pyrrolidin-2-ylidene]-1,3-dithiane (**73**)

A solution of azide (**34**) (466.3 mg, 2.16 mmol) in octane (5 ml) was heated

under reflux for 4 hours in an atmosphere of nitrogen. The reaction mixture was then cooled to 0°C and treated with pyridine (0.263 ml, 3.24 mmol) and trifluoracetic anhydride (0.367 ml, 2.6 mmol). After 30 minutes at 0°C and 1 hour at room temperature the solvent was removed by rotary evaporation and the product was purified by column chromatography (flash silica, 10-20% ethyl acetate in petrol) to give a mixture of (**73**) and (**74**) (ratio 3.57:1) (429.4 mg, 70.2%) which crystallized on standing, m.p. 52.7-56.7°C.

A sample of (**73**) was also prepared by adding a solution of N-(2,2,2-trifluoroacetyl) proline methyl ester (2.25 g, 10 mmol) in dichloromethane (20 ml) to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml). After stirring for 2 days at room temperature the reaction mixture was heated under reflux for 10 hours. The normal work-up procedure was followed by column chromatography (flash silica, 10-15% ethyl acetate in petrol) to give (**73**) (488.1 mg, 17.2%) as a colourless oil which crystallized on standing, m.p. 58-62°C (Found: C, 42.6; H, 4.37; N, 5.04; $C_{10}H_{12}F_3NOS_2$ requires C, 42.39; H, 4.27; N, 4.94%); υ_{max} 2930, 1700, 1600, 1460 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.02 (2H, quintet, J = 6.5 Hz), 2.11-2.20 (2H, m), 2.71 (2H, t, *J* = 7.9 Hz), 2.84 (2H, t, *J* = 6.3 Hz), 2.93 (2H, t, *J* = 6 Hz), 3.86 (2H, t, *J* = 7.2 Hz); peaks due to (**74**), 4.11 (2H, dt, *J* = 1.5, 7.7 Hz), 5.78 (1H, d, *J* = 1.5 Hz), 5.85 (1H, dt, *J* = 1.1, 1.8 Hz); *m/z* (70 eV E.I.) 283 (M^+, 50%), 250 (2), 236 (2), 222 (2), 209 (8), 186 (100).

1-(2,2,2-Trifluoroacetyl)pyrrolidine-2-carbothioic acid-S-(3-mercaptopropan-1-yl ester (**75**)

A solution of N-(2,2,2-trifluoroacetyl proline methyl ester (.2.5 g, 10 mmol) in dichloromethane (20 ml) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml) and stirred at room temperature for 2 days. Normal work-up followed by column chromatography (flash silica, 10-25% ethyl

acetate in petrol) gave (**75**) (1.177 g, 39%) as an oil.

A sample of (**75**) was also prepared by dissolving (**73**) (279.5 mg, 0.988 mmol) in a mixture of acetic acid (2 ml) and concentrated hydrochloric acid (2 drops) and heating the solution under reflux for 10 minutes. Water (5 ml) was then added and the product was extracted with ethyl acetate (2 x 5 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the residue was purified by column chromatography (flash silica, ethyl acetate in petrol) to give (**75**) (204.1 mg, 68.6%) as an oil; (Found; 194.04126, $C_7H_7NO_2F_3$ requires 194.04289, Δ = 3.5 ppm). υ_{max} 2950, 2570, 1710, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.40 (1H, t, J = 8.0 Hz), 1.89 (2H, quintet, J = 7.1 Hz), 1.97-2.34 (4H, m), 2.57 (2H, q, J = 7.2 Hz), 3.03 (2H, t, J = 7.1 Hz), 3.63-3.92 (2H, m), 4.74 (1H, dd, J = 3.3, 8.3 Hz); *m/z* (70 eV E.I.) 301 (M^+, 2%), 220 (2), 205 (5), 194 (10), 166 (100),

2-[$\Delta^{2,3}$-Pyrroline-1-(carboxylic acid ethyl ester)-2-yl]-1,3-dithiane (**76**)

A solution of (**34**) (227.2 mg, 1.06 mmol) in *n*-octane (3 ml) was heated under reflux in an atmosphere of nitrogen for 4 hours then allowed to cool to room temperature. The reaction mixture was then cooled in ice, diluted with dichloromethane (3 ml) and treated with triethylamine (101 mg, 1.0 mmol) and ethyl chloroformate (110 mg, 1.0 mmol). After stirring for three days at room temperature the solvent was removed and the major product was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to yield (**76**) (73.7 mg, 26.9%) as a colourless oil; (Found: m^+, 259.0689; $C_{11}H_{17}NO_2S_2$ requires m, 259.0699, Δ = 4.5 ppm); υ_{max} 2900, 1700, 1630, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25 (3H, t, J = 7 Hz), 1.80-1.93 (1H, m), 2.04-2.14 (1H, m), 2.5 (2H, m), 2.8-3.0 (4H, m), 3.83 (2H, t, J = 9 Hz), 4.13 (2H, q, J = 7 Hz), 5.40 (1H, dt, J = 1, 3 Hz), 5.73 (1H, broad); δ_C (68 MHz; $CDCl_3$) 14.53 (CH_3), 25.59 (CH_2), 26.99 (CH_2), 31.03 (CH_2), 42.26 (CH), 48.04 (CH_2),

61.04 (CH_2), 111.80 (CH), 152.63; *m/z* (low eV E.I.) 259 (M^+, 100%), 225 (5), 173 (30).

2-[$\Delta^{2,3}$-Pyrroline-1-(carboxylic acid 2-naphthyl ester)-2-yl]-1,3-dithiane (**77**)

A solution of (**34**) (337.8 mg, 1.57 mmol) in *n*-octane (3 ml) was heated under reflux for 4 hours then cooled to 0°C, diluted with dichloromethane (3 ml) and treated with pyridine (250 mg, 3.14 mmol) and 2-naphthyl chloroformate (340mg, 1.65 mmol). After stirring for 15 mins the solvent was removed by rotary evaporation and methanol was added which caused crystallisation of the product to give (**77**) (105.3 mg, 19%). A further protion of (**77**) (180.6 mg, 32%) was obtained from the mother liquor (total yield 51%) m.p. 149.2-150.2°C; (Found: C, 64.0; H, 5.21; N, 3.54; $C_{19}H_{19}NO_2S_2$ requires C, 63.83; H, 5.36; N, 3.92%); υ_{max} 2900, 1700, 1620, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.65 (2H, broad), 1.85-1.95 (1H, m), 2.05-2.17 (1H, m), 2.67 (2H, m), 2.8-3.2 (4H, m), 4.13 (2H, t, J = 9 Hz), 5.58 (1H, dt, J = 0.5, 2.5 Hz), 5.84 (1H, broad), 7.3-7.9 (7H, m); *m/z* (low eV E.I.) 357 (M^+, 100%), 314 (65), 214 (75), 144 (25).

On standing in $CDCl_3$, (**77**) was hydrolysed to the corresponding amino ketone (**78**); δ_H (270 MHz; $CDCl_3$) 1.95 (2H, quintet, J = 7 Hz), 2.0-2.15 (2H, m), 2.55-2.65 (2H, ddd, J = 3, 5, 15 Hz), 2.30 (2H, t, J = 7 Hz), 3.2-3.3 (2H, ddd, J = 3.5, 11, 15 Hz), 3.35 (2H, q, J = 6 Hz), 4.26 (1H,), 5.30 (1H, broad), 7.3-7.9 (7H, m).

2-[1-(4-Methylphenylsulphonyl)pyrrolidin-2-ylidene]-1,3-dithiane (**79**)

A solution of (**34**) (215 mg, 1.0 mmol) in *n*-octane was heated under reflux in an atmosphere of nitrogen for four hours. The reaction mixture was then cooled in ice, diluted with dichloromethane and treated with tosyl chloride (191 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol). After stirring at room temperature the major product was separated by column chromatography (Kieselgel 60H, 5% ethyl acetate in

petrol) which gave a mixture of (**79**) and N,N-diethyl-N-(4-methylphenylsulphonyl)amine (**80**) [91.6 mg, ratio 1:1.8, 12.2% of (**79**)]; υ_{max} 2950, 2920, 1650, 1590, 1450, 1330 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.93-2.06 (4H, m), 2.33 (3H, s), 2.75-2.83 (4H, m), 3.01 (2H, t, J = 7 Hz), 4.06-4.12 (2H, m), 7.12, (2H, d, J = 7.9 Hz, part of AA'BB'), 7.42 (2H, d, J = 8.1 Hz, part of AA'BB'); peaks due to (**80**); 1.12 (6H, t, J = 7 Hz), 2.41 (3H, s), 3.22 (4H, q, J = 7 Hz), 7.28, (2h, d, J = 8.0 Hz, part of AA'BB'), 7.68 (2H, d, J =8.2 Hz, part of AA'BB'); δ_C (68 MHz; $CDCl_3$) 20.92 (CH_3), 21.96 (CH_2), 26.86 (CH_2), 28.15 (CH_2), 33.80 (CH_2), 37.17 (CH_2), 62.08 (CH_2), 128.60 (CH), 129.71 (CH), 142.78, 172.68; peaks due to (**80**); 14.04 (CH_3), 21.34 (CH_3), 41.91 (CH_2), 126.92 (CH), 129.48 (CH); *m/z* (C.I.) 326 (MH^+-16, 1%), 268 (MH^+-74, 1), 228 (MH^+ for (**80**), 100).

S,S'-Trimethylenebis[-1-(4-methylphenylsulphonyl)pyrrolidin e-2-carbothioic acid (**82**)

A solution of (**81**) (849 mg, 3 mmol) in dichloromethane (6 ml) was added to a freshly prepared solution of BDP (3 mmol) in dichloromethane/toluene (2:1, 9 ml) and stirred at room temperature for 2 days. The normal work-up procedure was followed and gave two major (more polar) products and three minor (less polar) products, as judged by TLC. Column chromatography gave (**82**) (103.5 mg, 11.4%) and a mixture of (**82**) and (**83**) (55.0 mg, 6.0%); δ_H (270 MHz; $CDCl_3$) 1.65-2.0 (10H, m), 2.48 (6H, s), 2.70-2.98 (4H, m), 3.18-3.35 (2H, m), 3.56-3.65 (2H, m), 4.38 (2H, dd, J = 4, 13 Hz), 7.38 (2H, d, J = 8.4 Hz, part of AA'BB'), 7.80 (2H, d, J = 8.4 Hz, part of AA'BB'), peaks due to diastereomer (**83**); 2.47 (s), 4.60 (dd, J = 7, 14 Hz), 7.36, (2H, d, J = 8.2 Hz, part of AA'BB'), 7.88 (2H, d, J = 8.2 Hz, part of AA'BB'). Compounds (**82**) and (**83**) were not characterized by elemental analysis or high resolution mass determination.

2-Methyl-2-[1-(4-methylphenylsulphonyl)pyrrolidin-2-yl]-1,3-dithiane (84)

A solution of (81) (1.13 g, 4 mmol) in dichloromethane (8 ml) was added to a freshly prepared solution of BDP (4 mmol) in dichloromethane/toluene (2:1, 12 ml) and stirred at room temperature for 12 hours. TLC analysis of the reaction mixture revealed five products as described in the preparation of (82). The reaction mixture was then heated under reflux at 65-70°C for 2 days, which caused a slight decrease in the relative amounts of the two more polar products. The reaction was worked up by the normal procedure and the least polar compound was isolated by column chromatography (flash silica, 20-40% ethyl acetate in petrol to give (84) (70.9 mg, 50%) as an oil; υ_{max} 2900, 1650, 1580, 1420 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.80-2.03 (6H, m), 2.11 (3H, s), 2.43 (3H, s), 2.60-3.40 (5H, m), 3.61 (1H, ddd, J = 2.5, 9, 12 Hz), 4.54 (1H, dd, J = 4.5, 8 Hz), 7.30 (2H, d, J = 8.4 Hz, part of AA'BB'), 7.38 (2H, d, J = 8.4 Hz, part of AA'BB') (contains impurities); *m/z* (C.I.) 358 (MH^+, 3%), 342 (2), 299 (15), 224 (10), 204 (100). Compound (84) was not characterized by elemental analysis or high resolution mass determination.

2-Hydroxy-1-(4-methylphenylsulphonyl)-2-[1-(4-methylphenylsulphonyl)pyrrolidin-2-on-3-yl]pyrrolidinone (88)

A solution of (2) (192 mg, 1.0 mmol) in dry THF (2 ml) was cooled to -60°C under an atmosphere of nitrogen and treated with a solution of *n*-butyl lithium (0.69 ml, 1.1 mmol) then allowed to warm to 0°C. The resulting anion was cooled to -78°C and then a solution of (87) (239 mg, 1.0 mmol) in THF (4 ml) was added dropwise. The reaction mixture was stirred for 1 hour at -78°C and then allowed to warm to room temperature and stirred for 18 hours. Saturated aqueous ammonium chloride was added and the product was extracted with ethyl acetate (3 portions). The organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation and the product was isolated by column chromatography to give (88)

(109.9 mg, 46%) which could be recrystallized from benzene/petrol, m.p. 135.7-136.7°C; (Found: C, 54.9; H, 5.47; N, 5.78; $C_{22}H_{26}N_2O_6S_2$ requires C, 55.21; H, 5.48; N, 5.85%); υ_{max} 3270, 2900, 1720, 1680, 1590, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.43-1.63 (3H, m), 1.86-2.03 (1H, m), 2.24 (3H, s), 2.26 (3H, s), 2.25-2.49 (1H, m), 2.55-2.78 (3H, m), 3.43 (1H, dd, *J* = 7.5, 9 Hz), 3.58-3.70 (1H, m), 3.78 (1H, dt, *J* = 5, 9 Hz), 4.59 (1H, t, *J* = 6.5 Hz), 7.12, (2H, d, *J* = 8.4 Hz, part of AA'BB'), 7.16 (2H, d, *J* =8.4 Hz, part of AA'BB'), 7.52 (2H, d, *J* = 8.1 Hz, part of AA'BB'), 7.70 (2H, d, *J* = 8.4. Hx, part of AA'BB'); *m/z* (C.I.) 461 (MH^+-18, 2%), 323 (0.5), 307 (2), 2.80 (4), 240 (100).

2-[4-(N-2,2-Dimethylpropanoyl)amino-1-oxobutyl]-1,3-dithiane (**92**)

A solution of (**71**) (146.5 mg, 0.54 mmol) in a mixture of acetic acid (1 ml) and concentrated hydrochloric acid (1 drop) was heated under reflux for 5 minutes. Water (2 ml) was added and the product was extracted with ethyl acetate (3 x 3 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation then the residue was purified by column chromatography (60% ethyl acetate in petrol) to give (**92**) (138.5 mg, 88.6%) as an oil; (Found: C, 53.4; H, 8.36; N, 4.78; $C_{13}H_{23}NO_2S_2$ requires C, 53.94; H, 8.01; N, 4.84); (Found: m^+, 289.11599, $C_{13}H_{23}NO_2S_2$ requires m, 289.11702, Δ = 3.0 ppm); υ_{max} 3500 (broad), 2950, 2600 (broad), 1720, 1640, 1500 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.19 (9H, s), 1.86 (2H, quintet, *J* = 6.8 Hz), 2.00-2.17 (2H, m), 2.60 (2H, ddd, *J* = 3.3, 5.7, 13.8 Hz), 2.73 (2H, t, *J* = 6.8 Hz), 3.22 (2H, ddd, *J* = 3.3, 106, 14.0 Hz), 3.27 (2H, q, *J* = 7.8 Hz), 4.25 (1H, s), 5.93 (1H, broad); *m/z* (70 eV E.I.) 289 (M^+, 20%), 220 (5), 205 (10), 170 (10), 154 (5), 119 (100).

5-Azidohexanoic acid methyl ester (**97**)

Cyclohexane-1,3-dione (11.2 g, 100 mmol) was hydrolysed using the known

procedure[142] to give 5-oxohexanoic acid which was esterified by dissolving in dry methanol, cooling to 0°C and adding thionyl chloride to give 5-oxohexanoic acid methyl ester. This compound was reduced using sodium borohydride in dry methanol at 0°C. The product was purified by chromatography to give 5-hydroxyhexanoic acid methyl ester (**98**) (6.42 g, 44 mmol), which contained an impurity. A solution of (**98**) (1.46 g, 10 mmol) in dichloromethane was cooled to 0°C and treated with tosyl chloride (1.91 g, 10 mmol) and pyridine (3.23 ml, 40 mmol). After warming to room temperature and stirring overnight the solvent was removed and the product was purified by chromatography to give the tosylate of (**98**) (2.251 g, 75%); υ_{max} 2950, 1720, 1580 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25 (3H, d, *J* = 6 Hz), 1.51-1.60 (4H, m), 2.20-2.25 (2H, m) 2.44 (3H, s), 3.64 (3H, s), 4.61 (1H, sextet, J = 6 Hz), 7.34 (2H, d, *J* = 8.0 Hz, part of AA'BB'), 7.78 (2H, d, *J* =8.2 Hz, part of AA'BB'). Compound (**98**) was not characterized by elemental analysis or high resolution mass determination.

The tosylate (**98**) (2.151 g, 7.17 mmol) was dissolved in DMF (20 ml) and treated with sodium azide (2.0 g, 30.8 mmol). The reaction mixture was then heated at 120°C in an oil bath under reflux for 3 hours. After cooling, water (40 ml) was added and the product was extracted with petrol (3 x 25 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation to give (**97**) (1.127 g, 91.9%) as a colourless oil. (Found: m^+, 171.1026, $C_7H_{13}N_3O_2$ requires m, 171.1007, Δ = 10.5 ppm); υ_{max} 2930, 2080, 1720, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.27 (3H, d, *J* = 6.5 Hz), 1.48-1.53 (2H, m), 1.60-1.85 (2H, m), 2.34 (2H, t, *J* = 7.5 Hz), 3.45 (1H, sextet, *J* = 6.5 Hz), 3.68 (3H, s); δ_C (68 MHz; $CDCl_3$) 19.17 (CH_3), 21.31 (CH_2), 33.41 (CH_2), 35.32 (CH_2), 51.38 (CH), 57.44 (CH_3), 173.46; *m/z* (70 eV E.I.) 171 (M^+, 10%), 139 (15), 129 (100), 11 (25).

2-(4-Azidopent-1-ylidene)-1,3-dithiane (**99**)

A solution of (**97**) (445 mg, 2.6 mmol) in dichloromethane (5 ml) was added

to a freshly prepared solution of BDP (2.6 mmol) in toluene/dichloromethane (1:2, 5 ml) at room temperature. After stirring for 2 days at room temperature the normal work-up procedure was followed and the product was purified by column chromatography (flash silica, 2-6% ethyl acetate in petrol) to give (**99**) (379.5 mg, 65.6%) as an oil. (Found: m^+-N_2, 201.0657, $C_9H_{15}NS_2$ requires 201.0644, Δ = 5.3 ppm); υ_{max} 2900, 2060, 1570, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.27 (3H, d, J = 6.5 Hz), 1.50-1.66 (2H, m), 2.12-2.20 (2H, m), 2.31 (2H, q, J = 7.5 Hz), 2.86 (4H, 2 x t, J = 6.5 Hz), 3.47 (1H, sextet, J = 6.5 Hz), 5.90 (1H, t, J = 7.5 Hz); δ_C (68 MHz; $CDCl_3$) 19.36 (CH_3), 25.10 (CH_2), 25.95 (CH_2), 29.48 (CH_2), 30.20 (CH_2), 35.26 (CH_2), 57.34 (CH), 132.04 (CH); *m/z* (70 eV E.I.) 201 (M^+-N_2, 1%), 186 (1), 159 (2), 145 (2), 143 (2), 119 (100).

2-(5-Methylpyrrolidin-2-yl)-1,3-dithiane (**101**)

A solution of (**99**) (155.6 mg, 0.679 mmol) in octane was heated under reflux in an atmosphere of nitrogen for 4 hours. The reaction mixture was allowed to cool to room temperature then cooled in an ice bath and diluted with dry methanol. Sodium borohydride (90 mg, 1.40 mmol) was added and after 30 minutes water was added and the product was extracted 3 times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulphate, filtered, concentrated by rotaty evaporation and then the product was isolated by column chromatography (0-80% methanol in ethyl acetate) to give (**101**) (115 mg, 80.9%) as an oil. (Found : m^+-dithianyl, 84.0816, $C_5H_{10}N$ requires 84.0813, Δ = 3.1 ppm), υ_{max} 3300 (broad), 2950, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.17, 1.18 (3H, 2 x d, J = 6.5, 6 Hz), 1.28-1.37 (1H, m), 1.77-2.13 (5H, m), 2.74 (1H, broad), 2.78-2.92 (4H, m), 3.17-3.22, 3.29-3.38 (1H, 2 x m), 3.41, 3.59 (1H, 2 x d, J = 7.5, 7.5 Hz); m/z (70 eV E.I.) 119 (5%), 84 (100)

2-[5-Methylpyrrolidine-1-(carboxylic acid phenylmethyl ester)-2-ylidene]-1,3-dithiane (**102**)

A solution of (**99**) (193.1 mg, 0.843 mmol) in octane (4 ml) was heated under reflux in an atmosphere of nitrogen for 2.5 hours after which (**99**) was absent and a more polar compound had formed cleanly. The reaction mixture was cooled in an ice bath and diluted with dichloromethane (4 ml). Pyridine (133 mg, 1.7 mmol) and benzyl chloroformate (174 mg, 1.01 mmol) were added which led to a new product. The solvent was removed and the product was isolated by column chromatography (flash silica, ethyl acetate and petrol) to give (**102**) as an oil (73.3 mg, 26%); (Found: m^+, 335.1029, $C_{17}H_{21}NO_2S_2$ requires m, 335.1012, $\Delta = 4.4$ ppm); υ_{max} 2900, 1680, 1590, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (3H, d, $J = 6.5$ Hz), 1.42-1.50 (1H, m), 2.08-2.20 (3H, m), 2.41 (1H, ddd, $J = 8.5, 9.5, 15$ Hz), 2.62 (1H, dt, $J = 14, 6$ Hz), 2.74 (1H, dt, $J = 13, 4.5$ Hz), 2.82-2.97 (3H, m), 4.22 (1H, sextet, $J = 6$ Hz), 5.07-5.40 (2H, m), 7.26-7.41 (5H, m); δ_C (68 MHz; $CDCl_3$) 21.99 (CH_3), 25.27 (CH_2), 29.52 (CH_2), 30.20 (CH_2), 30.78 (CH_2), 31.04 (CH_2), 56.63 (CH_2), 67.33 (CH_2), 127.89 (CH), 128.05 (CH), 128.31 (CH), 136.36, 139.83, 153.00; *m/z* (70 eV E.I.) 335 (M^+, 10%), 244 (15), 200(20), 91 (100).

5-Azido-1,1-bis (phenythio)pent-1-ene (**103**)

A mixture of alcohol (**114**) and the correspondig α-adduct (272 mg, 0.9 mmol), prepared from (**106**) and ethylene oxide, was dissolved in THF (10 ml) at 0°C and treated with triphenyl phosphine (262 mg, 1 mmol), DEAD (174 mg, 1 mmol) and a solution of diphenylphosphoryl azide (275 mg, 1 mmol) in THF (2 ml). After warming to room temperature and stirring for 12 hours the solvent was removed by rotary evaporation and was the product was isolated by column chromatography (flash silica, ethyl acetate in petrol) to give the mixture of azides (**103**) amd (**108**) (193.5 mg, 66%). A pure sample of (**103**) was prepared using alcohol (**114**) obtained from δ-valerolactone and aluminium tris(phenylthiolate). The alcohol (**114**) (1.498 g, 4.96

mmol) was subjected to the conditions described above which gave azide (**103**) (1.272 g, 78.4%) as a colourless oil; (Found: m^+-N_2, 299.0792, $C_{17}H_{17}NS_2$ requires m-N_2, 299.0801, Δ = 3.7 ppm); υ_{max} 3050, 2900, 2070, 1570 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.72 (2H, quintet, *J* = 7.3 Hz), 2.52 (2H, q, *J* = 7.2 Hz), 3.29 (2H, t, *J* =- 6.9 Hz), 6.26 (1H, t, *J* = 7.3 Hz), 7.06-7.64 (10H, m); *m/z* (70 eV E.I.) 299 (M^+-N_2, 1%), 275 (7), 218 (80), 190 (35), 154 (25), 131 (25), 121 (30), 109 (100).

5-Azidopentanethioic acid-S-phenyl ester (**105**)

A solution of (**43**) in dichloromethane was added to a preformed mixture of thiophenol and trimethylaluminium (ratio 1:1) in dichloromethane/toluene and stirred for 12 hours at room temperature which gave two products. The reaction was worked-up using the normal procedure and the products were isolated by column chromatography (flash silica, ethyl acetate in petrol). The more polar product was (**105**); υ_{max} 2900, 2070, 1690, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.6-1.85 (4H, m), 2.70 (2H, t, *J* = 7.0 Hz), 3.30 (2H, t, *J* = 6.7 Hz), 7.41 (5H, m); *m/z* (C.I.) 236 (MH^+, 70%), 208 (10), 193 (15), 126 (100). Compound (**105**) was not characterized by elemental analysis or high resolution mass determination.

5-Azido-3,3-bis(phenylthio)pent-1-ene (**108**)

Azide (**108**) was prepared as a 1:1 mixture with (**103**). (See preparation of (**103**)). Data for (**108**); δ_H (270 MHz; $CDCl_3$) 2.0 (2H, t, J = 6.9 Hz), 3.29 (2H, t, *J* = 6.9 Hz), 4.76 (1H, d, *J* = 17.4.Hz), 5.02 (1H, d, *J* = 10.8 Hz), 5.83 (1H, dd, *J* = 10.6, 17.3 Hz), 7.0-7.6 (10H, m).

2-Methyl-3,3-bis(phenylthio)pyrrolidine (**110**)

The mixture of azides (**103**) and (**108**) (180 mg, 0.55 mmol) was dissolved in

octane (2 ml) and heated under reflux for one hour. After this time one component of the mixture was absent and a new product had formed. The reaction mixture was cooled in ice and dry methanol (2 ml) was added followed by sodium borohydride (40 mg, 1 mmol). After stirring for 30 minutes water was added, the product was extracted with ether (3 portions) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The product was isolated by column chromatography (flash silica, 0-20% methanol in ethyl acetate) to give (**110**) (9.1 mg, 5.5%) as a yellow oil; (Found: m^+, 301.0959, $C_{17}H_{19}NS_2$ requires m, 301.0957); δ_H (270 MHz; $CDCl_3$) 1.31 (3H, d, J = 6.6 Hz), 1.79 (1H, dt, J = 8.6, 13.9 Hz), 1.92 (1H, ddd, J = 3.8, 8.2, 13.9 Hz), 2.33 (2H, broad), 2.76 (1H, ddd, J = 3.6, 9.5, 12 Hz), 3.01 (2H, dt, J = 8.2, 11.4 Hz), 3.19 (1H, q, J = 6.6 Hz), 7.29-7.72 (10H, m); *m/z* (70 eV E.I.) 301 (M^+, 2%), 245 (2), 218 (5), 192 (100).

5-Hydroxy-1,1-bis(phenylthio)pent-1-ene (**114**)

A solution of (**106**) (516 mg, 2.0 mmol) in THF (5 ml) was added to a freshly prepared solution of LDA (2.2 mmol) in THF (5 ml) at -78°C under an atmosphere of nitrogen. The solution was allowed to warm to -40°C resulting in a bright orange colour, then cooled to -78°C and gaseous etylene oxide (excess) from a cylinder was passed over the reaction mixture in a stream of nitrogen. After warming to room temperature the reaction was quenched with water and the product was extracted with ethyl acetate (3 portions). The combined organic extracts were dried under anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and then the product was isolated by column chromatography (flash silica, ethyl acetate in petrol) to give a mixture of the γ-adduct (**114**) and the corresponding α-adduct.

A sample of (**114**) was also prepared as follows; aluminium tris(phenylthiolate) (20 mmol) was prepared by refluxing a mixture of trimethyl aluminium (2.0M in toluene, 10 ml, 20 mmol) and thiophenol (6.0 ml, 60 mmol) in dry

toluene (30 ml) for 48 hours under nitrogen. To this reagent was added a solution of δ-valerolactone (2.0 g, 20 mmol) in toluene (10 ml) and the solution was heated under reflux for 3 days. 15% aqueous sodium hydroxide (100 ml) was added and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and purified by column chromatography (flash silica, 20-50% ethyl acetate in petrol) to give (**114**) (1.499 g, 25%) as an oil; (Found: m^+, 302.0794, $C_{17}H_{18}OS_2$ requires m, 302.0796, Δ = 1.6 ppm); υ_{max} 3300-3500 (broad), 3050, 2900, 1570, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.47 (2H, quintet, *J* = 5.3 Hz), 1.73-1.85 (2H, m), 2.26-2.38 (2H, m), 4.05 (3H, t, *J* = 5.5 Hz), 7.15-7.65 (10H, m). (NMR indicates the ring-closed isomer); *m/z* (low eV E.I.) 302 (m^+, 50%), 193 (100), 175 (40), 110 935).

2-[Bis(phenylthio)methylene]pyrrolidine (**115**)

A solution of (**103**) (825.3 mg, 2.52 mmol) in octane (10 ml) was heated under reflux in an atmosphere of nitrogen for 6 hours which led cleanly to a new product. The product was purified by chromatography (flash silica, ethyl acetate in petrol) to give (**115**) (496.6 mg, 66.0%) as an oil; (Found: m^+, 299.0781, $C_{17}H_{17}NS_2$ m, requires 299.0801, Δ = 7.3 ppm); υ_{max} 3380, 3050, 2900, 1570, 1450 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 2.09 (2H, quintet, *J* = 7.2 Hz), 2.89 (2H, t, *J* = 7.7 Hz), 3.49 (2H, t, *J* = 6.8 Hz), 5.57 (1H, broad), 7.05-7.28 (10H, m); δ_C (68 MHz; $CDCl_3$) 23.81 (CH_2), 31.62 (CH_2), 47.16 (CH_2), 124.55 (CH), 134.84 (CH), 125.209 (CH), 125.62 (CH), 128.70 (CH), 128.83 (CH), 129.22, 137.82, 140.05, 169.5; *m/z* (low eV E.I.) 299 (M^+, 100%), 218 (40), 190 (35), 157 (30), 134 (40), 120 (60), 106 (40).

2-[Bis(phenylthio)methyl]pyrrolidine (**116**)

A solution of (**103**) (275 mg, 0.84 mmol) in octane (4 ml) was heated under reflux in an atmosphere of nitrogen for five hours. The solution was cooled in ice and

diluted with dry methanol (4 ml) then sodium borohydride (excess) was added. After several hours, a small amount of reduced product had formed. Water was added and the product was extracted with ether (3 portions). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The product was isolated by column chromatography (flash silica, 0-20% methanol in ethyl acetate) to give (**116**) (10 mg, 4.0%) as an oil; δ_H (270 MHz; $CDCl_3$) 1.72-2.00 (4H, m), 2.23 (1H, broad), 2.85-2.93 (1H, m), 3.05-3.14 (1H, m), 3.47 (1H, dt, J = 5.4, 7.2 Hz), 4.49 (1H, d, J = 5.3 Hz), 7.21-7.49 (10H, m). Compound (**116**) was not characterized by elemental analysis or high resolution mass determination.

1-Benzoyl-2-[bis(phenylthio)methylene]pyrrolidine(**117**)

A solution of (115) (200 mg, 0.67 mmol) in dichloromethane (5 ml) was cooled to 0°C and treated with pyridine (79 mg, 1.0 mmol), benzoyl chloride (104 mg, 0.74 mmol) and DMAP (5 mg). After warming to room temperature and stirring for 12 hours a major new product had formed. The solvent was removed by rotary evaporation and the product was isolated by column chromatography (10-25% ethyl acetate, flash silica) to give (**117**) (154.7 mg, 56.5%) as an oil; Compound (**117**) could also be prepared in one pot from azide (**103**) (1.271g, 3.89 mmol), by thermolysis in octane followed by acylation with benzoyl chloride, pyridine and dichloromethane under standard conditions. This gave (**117**) (821.6 mg, 52.4% overall yield); υ_{max} 3050, 2900, 1650, 1570 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.99 (2H, quintet, J = 7.5 Hz), 2.99 (2H, t, J = 8.0 Hz), 3.83 (2H, t, J = 7.3 Hz), 7.12-7.62 (10H, m); m/z (C.I.) 404 (MH^+, 30%), 404 (100), 190 (25), 123 (65), 105 (80). Compound (**117**) was not characterized by elemental analysis or high resolution mass determination.

(4R, 5R)-4-Azidomethyl-5-(1,3-dithian-2-ylidene)methyl-2,2-dimet hyl-1,3-dioxolane (**118**)

A solution of (**2**) (106 mg, 0.55 mmol) in dry THF (3 ml) was cooled to -60°C and treated with *n*-butyl lithium (1.34 ml, 0.55 mmol). The solution was allowed to warm to room temperature then cooled to -78°C and aldehyde (**127**) (93 mg, 0.50 mmol) was added as a solution in THF (2 ml). The reaction mixture was allowed to warm to room temperature over 1.5 hours then water (3 ml) was added. The product was extracted with ethyl acetate (3 x 5 ml) and the combined extracts were dried (anhydrous sodium sulphate), filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (10% ethyl acetate in petrol) to yield (**118**) (14.5 mg, 10.1%) as an oil which began to crystallize on standing; (Found: C, 46.0; H, 6.1; N, 11.5; $C_{11}H_{17}N_3O_2S_2$ requires C, 45.97; H, 5.95; N, 14.62%); (Found: m^+-CH_2N, $_3$230.0404, $C_{10}H_{14}O_2S_2$ requires 230.0434, Δ = -11.7 ppm); υ_{max} 2920, 2100, 1580, 1380 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.43 (3H, s), 1.48 (3H, s), 2.15-2.25 (2H, m), 2.80-3.07 (4H, m), 3.25 (1H, dd, *J* = 4, 10 Hz), 3.58 (1H, dd, *J* = 3, 10 Hz), 3.73 (1H, ddd, *J* = 3, 4, 4 Hz), 4.82 (1H, t, *J* = 7 Hz), 5.8 (1H, d, *J* = 7 Hz); *m/z* (C.I.) 288 (MH^+, 100%), 260 (45), 230 (85); (70 eV E.I.) 230 (M^+-N_3CH_3, 5%), 162 (10), 119 (100).

(4R, 5R)-4-Azidomethyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**125**)

A solution of diol (**122**) (6.117 g, 37.7 mmol) in dichloromethane was treated with pyridine (3.0 g, 37.7 mmol) and tosyl chloride (7.20 g, 37.7 mmol) which was added dropwise as a solution in dichloromethane according to a known procedure[148]. This gave a mixture of recovered diol (**122**), monotosylate (**123**) and ditosylate (**124**). The crude mixture was dissolved in dry DMF and heated at 140°C under reflux for 3 hours. The reaction mixture was treated with water and extracted with ethyl acetate (3 portions). The combined organic extracts were dried over anhydrous sodium sulphate,

filtered, concentrated by rotary evaporation and the product was isolated by column chromatography to give (**125**) (2.40 g, 34% overall); υ_{max} 3450 (broad), 3000, 2930, 2100, 1450, 1400 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.44 (3H, s), 1.46 (3H, s), 1.94 (1H, broad, t, *J* = 5 Hz), 3.33 (1H, dd, *J* = 5, 14 Hz), 3.56 (1H, dd, *J* = 5, 14 Hz), 3.6-3.65 (1H, m, broad), 3.76-3.87 (1H, m, broad), 3.95-4.14 (2H, m); *m/z* (C.I.) 188 (MH^+, 3%), 172 (12), 162 (95), 160 (100). The azide (**125**) was not characterized by elemental analysis or high resolution mass determination. Previous reports of the preparation of (**125**) by a similar[222] and a different[223] route did not include analytical data.

(4R,5R)-4,5-Bis(azidomethyl)-2,2-dimethyl-1,3-dioxolane (**126**)

Also isolated from the preparation of (**125**) was the less polar diazide (**126**); υ_{max} 3000, 2950, 2100, 1440, 1370 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.46 (6H, s), 3.29-3.38 (2H, m), 3.50-3.59 (2H, m), 3.99-4.09 (2H, m).

(4S, 5R)-5-Azidomethyl-4-formyl-2,2-dimethyl-1,3-dioxolane (**127**)

A solution of oxalyl chloride (1.62 g, 12.76 mmol) in dichloromethane (29 ml) was cooled to -60°C under nitrogen and DMSO (1.972 ml, 12.76 mmol) in dichloromethane (5.0 ml) was added dropwise by syringe. After stirring for 2 minutes a solution of the alcohol (**125**) (2.17 g, 11.58 mmol) in dichloromethane (12 ml) was added dropwise. After stirring for a further 15 minutes at -60°C triethylamine (8.12 ml, 58 mmol) was added, the mixture was stirred at -60°C for 5 minutes and was then allowed to warm to room temperature. Water (150 ml) was added and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with 1N hydrochloric acid (10 ml), 1N sodium bicarbonate (10 ml) and brine (10 ml) then dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (flash silica,

35-50% ethyl acetate in petrol) to give (**127**) (1.64 g, 76.5%) as a colourless liquid; (Found: m^+-CH_3, 170.0580, $C_6H_8N_3O_3$ requires 170.0564, Δ = 8.4 ppm); (Found: m^+-CHO, 156.0772, $C_6H_{10}N_3O_2$ requires 156.0772; υ_{max} 3400 (broad), 3000, 2930, 2100, 1740, 1450, 1370 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.43 (3H, s), 1.55 (3H, s), 3.31-3.37 (1H, m), 3.63-3.69 (1H, m), 3.80-4.00 (1H, m), 4.24 (1H, t, J = 3 Hz, 9.81 (1H, s); *m/z* (70 eV E.I.) 170 (M^+-CH_3, 15%), 156 (M^+-CHO, 10), 143 (M^+-N_3, 5), 129 (25), 85 (25), 59 (30), 43 (100).

4-Bromobutanoic Acid Methyl Ester (**130a**)

A solution of 4-bromobutanoic acid (3.34g, 20 mmol) in dry methanol (20 ml) was cooled to 0°C and treated with thionyl chloride (4.0 ml, 50 mmol) which was added dropwise by syringe. The reaction mixture was allowed to warm to room temperature and then stirred for 18 hours. The solvent was removed by rotary evaporation, 5% aqueous potassium carbonate (20 ml) was added, and the product was extracted with ethyl acetate (3 x 25 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation to give (**130a**) (3.348 g, 92.5%) as a colourless liquid; υ_{max} 2950, 1730, 1440 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.8-2.3 (2H, m), 2.30 (2H, t, J = 5 Hz), 3.4 (2H, t, J = 6 Hz), 3.6 (3H, s). Spectral data are in agreement with those reported previously[215].

4-Azidobutanoic acid methyl ester (**131**)

A solution of (**130a**) (1.81 g, 10 mmol) in DMF (10 ml) was treated with sodium azide (1.3 g, 20 mmol) and potassium iodide (10 mg), and then stirred at room temperature for 24 hours. Water (30 ml) was added and the product was extracted with ethyl aceate (3 x 25 ml). The combined organic layers were washed with water (10 ml), dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation to give (**131**) (1.332 g, 93%) as a colourless liquid; υ_{max} 2950, 2090, 1730, 1440 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.6-2.0 (2H, m), 2.3 (2H, t, J = 6 Hz), 3.2 (2H, t, J = 7

Hz), 3.5 (3H, s). Spectral data are in agreement with those reported previously[216].

2-(3-Azidoprop-1-ylidene)-1,3-dithiane (**132**)

A solution of the ester (**131**) (318 mg, 2 mmol) in dichloromethane (4 ml) was added to a freshly prepared solution of BDP (2 mmol) in dichloromethane/toluene (2:1, 6 ml) at room temperature and then stirred for 2 days. The normal work-up procedure followed by chromatography (flash silica, 2-10% ethyl acetate in petrol) gave (**132**) (171.3 mg, 42.6%) as a colourless oil; (Found: m^+-CH_2N_3, 145.0132, $C_6H_9S_2$ requires 145.0145, Δ = -9.5 ppm); υ_{max} 2900, 2070, 1570, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.13-2.22 (2H, m), 2.53 (2H, q, J = 7 Hz), 2.890 (2H, t, J = 6 Hz), 2.893 (2H, t, J = 5.8 Hz), 3.31 (2H, t, J = 7 Hz), 5.90 (1H, t, J = 7.3 Hz); *m/z* (low eV E.I.) 201 (M^+, 40%), 145 (M^+-CH_2N_3, 70), 119 (100).

6-Bromohexanoic acid methyl ester (**133a**)

A solution of 6-bromoheanoic acid (3.9 g, 20 mmol) in dry methanol (20 ml) was cooled to 0°C and treated with thionyl chloride (4.0 ml, 50 mmol) which was added dropwise by syringe. After warming to room temperature the solution was stirred for 18 hours then concentrated by rotary evaporation. 5% Aqueous potassium carbonate (60 ml) was added and the product was extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation followed by high vacuum to give (**133a**) (3.96 g, 94.7%) as a colourless liquid; δ_H (60 MHz; $CDCl_3$) 1.3-1.9 (6H, m), 2.3 (2H, t, J = 7 Hz), 3.4 (2H, t, J = 7 Hz), 3.6 (3H, s). Spectroscopic data are in agrrement with those reported previously[217].

6-Azidohexanoic acid methyl ester (**133b**)

A solution of (**133a**) (2.09 g, 10 mmol) in DMF (10 ml) was treated with sodium azide (1.3 g, 20 mmol) and potassium iodide (10 mg) then stirred at room temperature for 18 hours. Water (30 ml) was added and the product was extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation followed by high vacuum to give (**133b**) (1.71 g, 100%) as a colourless liquid; υ_{max} 2940, 2090, 1730 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.3-1.8 (6H, m), 2.3 (2H, t, J = 7 Hz), 3.25 (2H, t, J = 7 Hz), 3.6 (3H, s). Spectroscopic data are in agreement with those reported previously[218].

2-(5-Azidopent-1-ylidene)-1,3-dithiane (**133**)

A solution of (**133b**) (1.71 g, 10 mmol) in dichloromethane (20 ml) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml) and stirred at room temperature for 48 hours. The normal work-up procedure was followed by column chromatography (Kieselgel 60H, 2-4% ethyl acetate in petrol) which gave (**133**) (1.521 g, 66.5%) as a pale yellow oil; (Found: m^+-N_2,201.0626, $C_9H_{15}NS_2$ requires 201.0644, Δ = -10.0 ppm); υ_{max} 2930, 2090, 1580, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.40-1.55 (2H, m), 1.57-1.75 (2H, m), 2.11-2.21 (2H, m), 2.25 (2H, q, J = 7.3 Hz), 2.84-2.88 (4H, m), 3.28 (2H, t, J = 7 Hz), 5.92 (1H, t, J = 7.4 Hz); *m/z* (C.I.) 230 (MH^+, 65%), 199 (100); (70 eV E.I.) 201 (M^+-N_2, 5%), 145 (40), 119 (100), 106 (35), 71 (50).

2-[Piperidine-1-(carboxylic acid phenylmethyl ester)-2-ylidene]-1,3-dithiane (**135**)

A solution of (**133**) (542.4 mg, 2.37 mmol) in octane (6 ml) was heated under reflux in an atmosphere of nitrogen for 24 hours which led cleanly to a new product. The reaction mixture was cooled in ice and treated with ether (10 ml), water (10 ml),

potassium carbonate (660 mg, 4.74 mmol) and benzyl chloroformate (490 mg, 2.84 mmol). After stirring for 3 hours the thermolysis product was absent and two new products had formed. The organic layer was separated and the aqueous layer was washed with ether. The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and purified by column chromatography (flash silica, ethyl acetate in petrol) to give (**135**) (411.9 mg, 52%) as an oil, followed by (**136**) (281.8 mg, 34%) as a white, amorphous solid. Data for (**135**); υ_{max} 2920, 1670, 1580, 1400 cm^{-1}; (Found: m^+, 335.10301, $C_{17}H_{21}NO_2S_2$ requires m, 335.10137, Δ = -5 ppm); δ_H (270 MHz; $CDCl_3$) 1.5-1.7 (4H, broad), 1.75-1.85 (2H, broad), 2.0-2.15 (2H, broad), 2.61-3.10 (6H, m), 5.15 (2H, s), 7.26-7.40 (5H, m); δ_C (68 MHz; $CDCl_3$) 23.06 (CH_2), 24.59 (CH_2), 25.30 (CH_2), 25.72 (CH_2), 29.16 (CH_2),. 29.74 (CH_2), 31.56 (CH_2), 47.00 (CH_2), 67.17 (CH_2), 118.49, 127.66 (CH), 128.15 (CH), 128.22 (CH), 136.75; *m/z* (low eV E.I.) 335 (M^+, 100%), 220 (15), 200(15), 106 (10), 100 (10)

5-(1,3-Dithian-2-yl)-5-oxopentan-1-ylcarbamic acid phenylmethyl ester(**136**)

For the preparation of (**136**) see (**135**) Data for (**136**); m.p. 51.2-52.2°C; (Found: C, 58.0; H, 6.58; N, 3.89%; $C_{17}H_{23}NO_3S_2$ requires C, 57.76; H, 6.56; N, 3.96%); υ_{max} 3350, 2900, 1680, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.49-1.57 (2H, m), 1.61-1.70 (2H, m), 1.94-2.14 (2H, m), 2.54-2.62 (2H, ddd, J = 3.4, 5.3, 13.9 Hz), 2.65 (2H, t, J = 7 Hz), 3.17-3.27 (2H, ddd, J = 3.4, 10.0, 13.8 Hz), 3.22 (2H, t, J = 6.6 Hz), 4.19 (1H, s), 4.83 (1H, s, broad), 5.09 (2H, s), 7.30-7.36 (5H, m); *m/z* (70 eV E.I.) 353 (M^+, 2%), 335 (1), 262 (10), 245 (3), 205 (3), 149 (6), 119 (100).

2-(Piperidin-2-yl)-1,3-dithiane (**137**)

A solution of (**133**) (921.4 mg, 4.023 mmol) in octane (8 ml) was heated under reflux in an atmosphere of nitrogen for 24 hours. The reaction mixture was then

cooled in ice, diluted with dry methanol (8 ml) and treated with sodium borohydride (304 mg, 8.0 mmol). After 30 minutes, at 0°C the thermolysis product was absent. Water (10 ml) was added and the product was extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with brine (2 ml), dried over anhydrous sodium sulphate, filtered and then concentrated by rotary evaporation. The residue was purified by column chromatography (flash silica, 0-60% methanol in ethyl acetate) to give (**137**) (471.0 mg, 57.7%) as an oil. (Found: C, 53.1; H, 8.7; N, 6.9; $C_9H_{17}NS_2$ requires C, 53.20; H, 8.37; N, 6.90%); υ_{max} 3300, 2900, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30-1.44 (3H, m), 1.55-1.63 (1H, m), 1.80-1.99 (3H, m), 2.05-2.18 (2H, m), 2.64 (1H, dt, J = 2.9, 11.8 Hz), 2.76-2.96 (4H, m), 3.09-3.14 (1H, m), 4.00 (1H, d, J = 6.6 Hz); δ_C (68 MHz; $CDCl_3$) 24.62 (CH_2), 26.11 (CH_2), 26.21 (CH_2), 29.55 (CH_2), 29.81 (CH_2), 30.42 (CH_2), 47.06 (CH_2), 53.22 (CH),, 59.36 (CH); *m/z* (C.I.) 204 (MH^+, 60%), 149 (5), 84 (100).

2-[Piperidine-1-(carboxylic acid-1,1-dimethylethyl ester)-2-yl]-1,3-dithiane(**138**)

A solution of (**133**) (1.476 g, 6.445 mmol) in octane (20 ml) was heated under reflux in an atmosphere of nitrogen for 24 hours, cooled in ice, diluted with dry methanol and then treated with sodium borohydride (260 mg, 6.5 mmol). After stirring for 2 hours the reaction mixture was diluted with water (20 ml) and the product was extracted with ether (3 x 20 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The crude product was dissolved in dichloromethane (20 ml) and treated with di-*tert*-butyldicarbonate (1.42.g, 6.5 mmol) and triethylamine (0.1 ml). After stirring ro 20 hours at room temperature the solvent was removed and the product was purified by column chromatography (flash silica, ethyl acetate in petrol) to give (**138**) (1.430 g, 73.2%) as a colourless oil which could be recrystallized from petrol, m.p. 94-96°C; (Found: C, 55.2; H, 8.45; N, 4.56; $C_{14}H_{25}NO_2S_2$ requires C, 55.44; H, 8.30, N, 4.62%0); υ_{max} 2950, 1680, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.47 (9H, s), 1.40-1.65

(5H, m), 1.90-2.20 (3H, m), 2.60-3.15 (5H, broad), 3.90-4.65 (3H, broad); *m/z* (C.I.) 304 (MH^+, 6%), 288 (3), 248 (40), 204 (65), 184 (65), 128 (100).

2[1-(4-Methylphenylsulphonyl)piperidin-2-yl]-1,3-dithiane (**139**)

A solution of (**137**) (471.0 mg, 2.32 mmol) was dissolved in dichloromethane (10 ml) under an atmosphere of nitrogen, cooled in ice and treated with tosyl chloride (443 mg, 2.32 mmol), pyridine (275 mg, 3,48 mmol) and DMAP (5 mg), then stirred by 0°C for 12 hours. The solvent was removed by rotary evaporation and the product was purified by column chromatography (flash silica, ethyl acetate in petrol) to give (**139**) (503.4 mg, 60.8%) as a colourless crystalline solid which was recrystallized from methanol, m.p. 111-112°C (Found; C, 53.8; H, 6.64; N, 3.93, $C_{16}H_{23}NO_2S_3$ requires C, 53.75; H, 6.48; N, 3.92%); υ_{max} 2950, 1600, 1470, 1340, 1160; δ_H (270 MHz; $CDCl_3$) 1.15-1.35 (1H, m), 1.36-1.55 (4H, m), 1.86-1.99 (1H, m), 2.00-2.12 (2H, m), 2.42 (3H, s), 2.68-2.83 (2H, m), 2.86-3.06 (3H, m), 3.73 (1H, broad), dd, J = 4, 14.8 Hz), 4.32-4.37 (2H, m), 7.29 (2H, d, J = 8.3 Hz, part of AA'BB'), 7.79 (2H, d, J = 8.3 Hz, part of AA'BB'); *m/z* (C.I.) 358 (MH^+, 85%), 252 (10), 238 (100), 213 (15).

1-(4-Methylphenylsulphonyl)piperidine-2-carboxaldehyde(**140**)

A solution of (**139**) (229.9 mg, 0.64 mmol) was dissolved in dichloromethane (10 ml) and treated with bis(trifluoroacetoxy)iodobenzene (305 mg, 0.71 mmol). After 5 minutes at room temperature water (5 ml) was added and the product was extracted with dichloromethane (2 x 10.ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the product was purified by column chromatography (flash silica, 15-30% ethyl acetate in petrol) to give (**140**) (169.3 mg, 73.8% corrected yield based on n.m.r. which showed 20% unreacted (**139**)); υ_{max} 2950, 2860, 1730, 1600, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30-1.60 (6H, m), 2.44 93H, s), 3.22 (1H, ddd, J = 3.0, 8.8, 12.6 Hz), 3.37 (1H, ddt, J =

1.5, 5.3, 13 Hz), 4.06 (1H, t, J = 5.0 Hz), 7.33 (2H, d, J = 8.2 Hz, part of AA'BB'), 7.69 (2H, d, J = 8.2 Hz, part of AA'BB'), 9.56 (1H, d, J = 0.5 Hz); *m/z* 268 (MH^+, 80%), 238 (100), 155 (30), 91 (60). Compound (**140**) was not characterized by elemental analysis or high resolution mass determination. A previous report of (**140**) contained no analytical data[219].

1-(4-Methylphenylsulphonyl)pipecolic acid (**141**)

A solution of (**140**) (149 mg, containing 20% (**139**), 0.418 mmol w.r.t. (**140**) was dissolved in a mixture of water, acetonitrile and tetrachloromethane (3:2:2, 2 ml total) and treated with sodium periodate (360 mg, 1.67 mmol) and ruthenium trichloride (2 mg). The reaction mixture was stirred rapidly for 18 hours then the product was extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the product was isolated by column chromatography (flash silica, 0-40% methanol in ethyl acetate) to give (**141**) (84.7 mg, 71.5%) as a crystalline solid.

A sample of (**141**) was also prepared by dissolving pipecolic acid (1.29 g, 10 mmol) and sodium hydroxide (800 mg,20 mmol) in ether (10 ml) and water (10 ml), adding tosyl chloride (1.91 g, 10 mmol) and stirring vigorously for 3 hours. The organic layer was then removed and the aqueous layer was acidified to congo red with 2N hydrochloric acid, causing precipitation of (**141**) (75.6%) which could be recrystallized from ethyl acetate/petrol to give plates, m.p. 100-101°C; (Found: C, 54.9; H, 6.07; N, 4.88, $C_{13}H_{17}NO_4S$ requires C, 55.10; H, 6.05; N, 4.94%); υ_{max} 2900, 2500-3200 (broad), 1720, 1600, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25-1.55 (2H, m), 1.60-1.80 (3H, m), 2.1-2.2 (1H, m), 2.42 (3H, s), 3.19 (1H, dt, J = 2.5, 12.8 Hz), 3.75 (1H, d, broad, J = 12.4 Hz), 4.78 (1H, d, J = 5.1 Hz), 7.28 (2H, d, J = 8.3 Hz, part of AA'BB'), 7.69 (2H, d, J = 8.3 Hz, part of AA'BB'); *m/z* (70 eV E.I.) 238 (M^+-CO_2H, 100%); (C.I.) 284 (MH^+, 25%), 238 (100), 155 (15), 91 (35). A previous report of (**141**)

gave analytical data only for the dicyclohexylamine salt[153]; m.p. of dicyclohexylamine salt of (**141**); 186-188°C (lit; 166-168°C)

(2S, 3S, 4R)-3,4-Dihydroxyproline (**148**)

A solution of (**171**) (16.8 mg, 0.585 mmol) was dissolved in a mixture of TFA and methanol (10:1, 2 ml) and stirred at room temperature for 5 days. The solvent was removed by rotary evaporation to give (**172b**) which was purified by ion exchange chromatography (DOWEX 5 x 80-100, acidic form). A solution of (**172b**) in water (1 ml) was applied to the column which was then eluted with water followed by 2N aqueous pyridine to give (**148**) (5.3 mg = 62%) which crystallized on standing, m.p. 228-230°C (decomp)[lit;>220°C (decomp.)[155]]; υ_{max} 3450 (broad), 2900, 1600, 1450; δ_H (270 MHz; D_2O) 3.26 (1H, dd, J = 8.8, 12.1 Hz), 3.58 (1H, dd, *J* = 7.9, 11.8 Hz), 4.21 (1H, d, *J* = 4.1 Hz), 4.43-4.53 (2H, m); δ_C (68 MHz; D_2O) 47.8, 65.36, 71.4, 71.7, 171.2; *m/z* (C.I.) 148 (MH^+, 95%), 112 (45), 102 (100).

2-[(1R, 2R, 3R)-4-Azido-1,2,3-trihydroxybutan-1-yl)-1,3-dithiane (**154**)

A solution of (**153**) (6.3 g, 27.5 mmol) in dichloromethane (50 ml) was treated with 1,3-propanedithiol (6.0 ml, 60.5 mmol) and *p*-toluene sulphonic acid (100 mg). After stirring for 24 hours, the reaction mixture was concentrated to an oil and the product was purified by column chromatography (60-120 mesh silica, 10-100% ethyl acetate in petrol) to give (**154**) (5.64 g, 75%) as a colourless crystalline solid, which could be recrystallized from ethyl acetate/petrol, m.p. 121-122°C; (Found: m^+, 265.0544, $C_8H_{15}N_3O_3S_2$ requires m, 265.0552, Δ = 4.1 ppm); υ_{max} 3100-3500 (broad), 2900,2070, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.67-1.86 (2H, m), 2.69-2.76 (2H, m), 2.78-2.97 (2H, m), 3.21 (1H, dd, *J* = 3, 13 Hz), 3.32 (1H, dd, *J* = 8, 13 Hz), 3.60-3.66 (2H, m), 3.83-3.88 (1H, m), 4.37 (1H, d, *J* = 1.8 Hz), 5.06 (1H, d, *J* = 6 Hz), 5.19 (1H, d, *J* = 6 Hz), 5.40 (1H, d, *J* = 5.5 Hz). (Intensity of peaks at 5.06, 5.19, 5.40 reduced by

D_2O shake); *m/z* (70 eV E.I.) 265 (m^+, 1%), 251 (1), 220 (1), 205 (3), 167 (15), 149 (60), 119 (40), 43 (100).

2-[(1R, 2R, 3R)-4-Azido-1,2,3-tris(phenylmethyloxy)butan-1-yl)-1,3-dithiane (**155**)

A solution of (**154**) (450 mg, 1.70 mmol) in dry THF (10 ml) was cooled to -20°C under N_2 and treated with sodium hydride (290 mg, 7.65 mmol) and tetrabutylammonium iodide (5 mg). After stirring for 10 minutes, a solution of benzyl bromide (1.02 g, 5.95 mmol) in dry THF (5 ml) was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Water (5 ml) was added cautiously and the product was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation, and the product was isolated by column chromatography (Kieselgel 60H, 15% ethyl acetate in petrol) to give (**155**) (589.8 mg, 64.8%) as a colourless oil. υ_{max} 3000, 2900, 2080, 1600, 1490, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85-1.97 (1H, m), 2.02-2.11 (1H, m), 2.59-2.86 (4H, m), 3.24 (1H, dd, *J* = 3, 13 Hz), 3.47 (1H, dd, *J* = 7.5, 13 Hz), 3.74 (1H, dd, *J* = 4, 6 Hz), 3.91 (1H, dt, *J* = 3, 6 Hz), 4.01 (1H, dd, *J* = 3.6, 6 Hz), 4.47 (1H, d, *J* = 4.4 Hz), 4.60-4.95 (6H, m), 7.27-7.36 (15H, m); *m/z* (C.I.) 508 (mH^+-N_2 70%); (70 eV E.I.) 399 (2%), 388 (m^+-$PhCH_2$-CH_2N_3, 2), 302 (2), 251 (10), 149 (10), 119 (25), 91 (100). Compound (**155**) was not characterized by elemental analysis or high resolution mass determination.

(4R, 5R, 6R)-4-Azidomethyl-6-(1,3-dithian-2-yl)-5-hydroxy-2,2-dimethyl-1,3-dioxane (**156a**)

A solution of (**154**) (81.8 mg, 0.31 mmol) in acetone (5 ml) was treated with 2,2-dimethyoxypropane (0.5 ml) and *p*-toluene sulphonic acid (2 mg). After stirring for 24 hours, (**154**) was absent and a less polar product had formed. The solvent was

removed and the product was isolated by column chromatography (flash silica, 10-30% ethyl acetate in petrol) to give (**156a**) (64.3 mg, 68%) as a mixture of isomers. δ_H (200 MHz; $CDCl_3$) 1.26-1.53 (6H, 6xs), 2.0-2.1 (2H, m), 2.75-3.1 (4H, m), 3.35-3.55 (2H, m), 3.65-4.15 (2H, m), 4.15-4.5 (2H, m); *m/z* (C.I.) 305 (m^+, 5%), 280 (10), 278 (mH^+-28, 25), 220 (20), 119 (100).

(2R,3R,4R)-2-Azidomethyl-4-(1,3-dithian-2-yl)-3-hydroxy-1,5-dioxaspiro[5.5]undecan e (**156b**)

A solution of 1,1-dimethoxycyclohexane was prepared by stirring 1,4-dioxane (5 ml), cyclohexanone (3 ml), trimethylorthoformate (0.75 ml) and *p*-toluene sulphonic acid (10 mg) at room temperature for 2 hours[207]. To this solution was added (**154**) (265 mg, 1.0 mmol). After stirring at room temperature for 20 hours, (**154**) was absent and a mixture of at least two less polar compounds was present. The reaction mixture was neutralised with triethylamine, concentrated by rotary evaporation and the products were isolated by column chromatography (flash silica, 5-20% ethyl acetate in petrol) to give (**156b**) as a mixture of isomers (271 mg, 78%); (Found: m^+, 345.1216, $C_{14}H_{23}N_3O_3S_2$ requires m, 345.1179, Δ = 10.1 ppm); υ_{max} 3400 (broad), 2900, 2080, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28-1.66 (10H, m), 2.0-2.1 (2H, m), 2.54 (1H, broad), 2.7-3.1 (4H, m), 3.37-3.55 (2H,m), 3.8-4.6 (4H, m); *m/z* (low eV E.I.) 345 (m^+, 25%), 298 (25), 198 (30), 119 (100).

(2R, 4R, 5R, 6R)-4-Azidomethyl-6-(1,3-dithian-2-yl)-5-hydroxy-2-phenyl-1,3-dioxane (**157**)

As solution of (**154**) (1.527 g, 5.76 mmol) in dichloromethane (20 ml) was treated with benzaldehyde dimethoxy acetal (3 ml) and *p*-toluene sulphonic acid (5 mg). After stirring at room temperature for 30 minutes the reaction mixture was neutralised with triethylamine, the solvent was removed by rotary evaporation and the

product was isolated by column chromatography (flash silica, 20-30% ethyl acetate in petrol) to give (**157**) (1.890 g, 93.9%) as a colourless oil which crystallized on standing; m.p. 117.8-118.8°C (Found: C, 51.0; H, 5.46; N, 11.8; $C_{15}H_{19}N_3O_3S_2$ requires C, 50.97; H, 5.42; N, 11.89%); υ_{max} 3400, 2900, 2080, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.95-2.17 (2H, m), 2.7-2.85 (3H, m), 2.95-3.10 (2H, m), 3.55 (1H, dd, J = 5.5, 13 Hz), 3.65 (1H, dd, J = 3, 13 Hz), 3.91 (1H, ddd, J = 3, 5.5, 9 Hz), 3.94 (1H, t, J = 8.5 Hz), 4.02 (1H, dd, J = 4, 8.5 Hz), 4.29 (1H, d, J = 4 Hz), 5.65 (1H, s), 7.33-7.56 (5H, m); *m/z* (low eV E.I.) 353 (m^+, 20%), 307 (5), 119 (100).

2-[(2S, 3R)-4-Azido-2,3-dihydroxybutan-1-ylidene]-1,3-dithiane (**158**)

A solution of (**157**) (529 mg, 1.5 mmol) in dry THF (10 ml) was added dropwise to a freshly prepared solution of LDA (3.36 mmol) in THF (10 ml) at -78°C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature which led cleanly to more polar compound. The reaction was quenched with water (10 ml) and the product was extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the product was purified by column chromatography (30-50% ethyl acetate in petrol) to give (**158**) (264.7 mg, 73.4%) as a colourless oil; (Found: m^+, 247.0432; $C_8H_{13}N_3O_2S_2$ requires m, 247.0448, Δ = -6.9 ppm); υ_{max} 3200-3500 (broad), 2900, 2080, 1570, 1420 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.61 (1H, broad), 2.17 (2H, quintet, J = 6 Hz), 2.41 (1H, broad), 2.85-3.05 (4H, m), 3.37 (1H, dd, J = 4.2, 12.8 Hz), 3.43 (1H, dd, J = 6.8, 12.8 Hz), 3.78-3.87 (1H, m), 4.71 (1H, dd, J = 4.5, 8.5 Hz), 5.89 (1H, d, J = 8.5 Hz); *m/z* (70 eV E.I.) 247 (m^+, 5%), 219 (2), 173 (5), 161 (100), 119 (25), 87 (40).

(2R,3S)-3-Hydroxy-2-hydroxymethyl-1-oxa-6,10-dithiaspiro[4.5]decane (**159**)

Compound (**158**) (265 mg, 1.072 mmol) was dissolved in dichloromethane

(0.5 ml) then diluted with *n*-octane (3 ml), and solution was heated under reflux for 3 hours. This led to the formation of a less polar product which was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to give (**159**) (55.4 mg, 20.9%) as an oil; (Found: m^+, 247.0442; $C_8H_{13}N_3O_2S_2$ requires m, 247.0448, Δ = -3.0 ppm); υ_{max} 3300-3500, 2900, 2080, 1420 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.92-2.07 (1H, m), 2.13-2.23 (1H, m), 2.31 (1H, dd, *J* = 3.5, 14.5 Hz), 2.35 (1H, broad), 2.54 (1H, dd, *J* = 7, 14.5 Hz), 2.70-2.82 (2H, m), 3.38-3.56 (4H, m), 4.21-4.33 (2H, m); *m/z* (low eV E.I.) 247 (m^+, 100%), 186 (15), 106 (30), 30 (30).

(2R, 4R, 5R,6R)-4-Azidomethyl-5-(*tert*-butyldimethylsiloxy)-6-(1,3-dithian-2-yl)-2-phenyl-1,3-dioxane (**160**)

A solution of (**157**) (353 mg, 1 mmol) in DMF (2 ml) was treated with imidazole (170 mg, 2.5 mmol) and *tert*-butyldimethylsilyl chloride (181 mg, 1.2 mmol). After stirring for 12 hours at room temperature, the reaction had only proceeded to a small extent. The reaction mixture was then heated under reflux at 70°C for 9 hours which led to disappearance of (**157**). The product was isolated by column chromatography (flash silica, 2-10% ethyl acetate in petrol) which gave (**160**) (469.3 mg, 97.2%) as a colourless oil. (Found: C, 55.9; H, 7.53; N, 9.00; $C_{21}H_{33}N_3O_3S_2Si$ requires C, 53.92; H, 7.11; N, 8.98%); υ_{max} 2900, 2080, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.13 (3H, s), 0.19 (3H, s), 0.89 (9H, s), 1.95-2.05 (2H, m), 2.57-2.78 (2H, m), 3.04-3.16 (2H, m), 3.41 (1H, dd, *J* = 5.5, 14.5 Hz), 3.56 (1H, dd, *J* = 2.5, 14.5 Hz), 3.79 (1H, ddd, *J* = 2.5, 3.5, 8 Hz), 3.96 (1H, t, *J* = 8 Hz), 4.03 (1H, dd, *J* = 1.5, 8 Hz), 4.12 (1H, d, *J* = 1.5 Hz), 5.63 (1H, s), 7.32-7.53 (5H, m); δ_C (68 MHz; $CDCl_3$) -4.41 (CH_3) -3.93 (CH_3), 18.13, 25.26 (CH_2), 25.85 (CH_3), 28.80 (CH_2), 29.29 (CH_2), 43.79 (CH), 51.18 (CH_2), 64.68 (CH), 80.86 (CH), 88.23 (CH), 100.94 (CH), 126.17 (CH), 128.15 (CH), 128.83 (CH), 137.20; *m/z* (C.I.) 567 (m^+, 2%), 452 (1), 440 (10), 410 (35), 334 (10), 320 (10), 189 (30), 147 (40), 119 (100).

(2R,4R,5R,6R)-4-Azidomethyl-6-(1,3-dithian-2-yl)-2-phenyl-1 ,3-dioxane-5-carbonic acid phenyl ester (**161**)

A solution of the alcohol (**157**) (438 mg, 1.24 mmol) in dichloromethane (10 ml) was cooled to 0°C and treated with pyridine (0.5 ml) and phenyl chloroformate (214 mg, 1.49 mmol). After warming to room temperature and stirring for 18 hours, (**157**) was absent. The solvent was removed by rotary evaporation and the product was isolated by column chromatography (flash silica, 10-20% ethyl acetate in petrol) to give (**161**) (510.9 mg, 87.1%) which was recrystallized from ethyl acetate and petrol to give colourless needles m.p. 125.5-126.5°C (Found: C, 56.0; H, 4.89; N, 8.83; $C_{22}H_{23}N_3O_5S_2$ requires C, 55.80; H, 4.89; N, 8.87%); υ_{max} 2900, 2080, 1740, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.99-2.06 (2H, m), 2.63-2.72 (1H, ddd, *J* = 3.5, 7.5, 13.8 Hz), 2.72-2.81 (1H, ddd, *J* = 4.5, 6.5, 13.8 Hz), 3.05-3.18 (2H, m), 3.50 (1H, dd, *J* = 3.3, 13.5 Hz), 3.60 (1H, dd, *J* = 6.6, 13.5 Hz), 4.06-4.14 (1H, m), 4.09 (1H, d, *J* = 3.5 Hz), 4.34 (1H, dd, *J* = 3,4 9.3 Hz), 5.17 (1H, t, *J* = 9.3 Hz), 5.71 (1H, s), 7.17-7.56 (10H, m); *m/z* (C.I.) 473 (m^+, 3%), 446 (5), 352 (5), 308 (2), 248 (5), 202 (20), 119 (100).

(4S,5R)-4-(1,3-Dithian-2-ylidene)methyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**165**)

A solution of (**2**) (1.39 g, 7.22 mmol) in dry THF (15 ml) was cooled to -60°C under nitrogen and treated with *n*-butyl lithium (4.50 ml, 7.22 mmol) which was added dropwise by syringe. The solution was allowed to warm to 0°C then cooled to -78°C and a solution of (**164**) (525 mg, 3.28 mmol) in THF (10 ml) was added dropwise. The reaction was allowed to warm to room temperature, then saturated aqueous sodium chloride (10 ml) was added and the product was extracted with ethyl acetate (3 x 15 ml). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The residue was purified by

column chromatography (flash silica, 25-60% ethyl acetate in petrol) to give (**165**) (659.5 mg, 76.7%) as an oil; (Found: m^+, 262.0685; $C_{11}H_{18}N_3O_3S_2$ requires m, 262.0697, Δ = -4.9 ppm); υ_{max} 3300-3500, 2900, 1570, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.34 (3H, s), 1.53 (3H, s), 1.87-2.18 (2H, m), 2.04 (1H, dd, *J* = 4.2, 13.7 Hz), 2.24 (1H, dd, *J* = 6.4, 13.8 Hz), 2.56-2.66 (2H, m), 3.08 (1H, ddd, *J* = 2.8, 12.6, 14 Hz), 3.39 (1H, ddd, *J* = 2.8, 12.6, 13.9 Hz), 4.03-4.16 (3H, m), 4.41 (1H, ddd, *J* = 5.4, 5.9, 6.1 Hz); δ_C (68 MHz, $CDCl_3$) 24.74 (CH_2), 26.1 (CH_2), 26.1 (CH_3), 26.76 (CH_2), 27.99 (CH_3), 39.89 (CH_2), 62.73 (CH_2), 69.38 (CH), 70.66 (CH), 85.43, 108.92; *m/z* (low eV E.I.) 262 (m^+, 100), 217 (15), 188 (40), 161 (20), 132 (25), 128 (30).

(4S,5R)-4-Azidomethyl-5-(1,3-dithian-2-ylidene)methyl-2,2-dimethyl-1,3-dioxolane (**166**)

A solution of (**165**) (658 mg, 2.51 mmol) in dry THF (5 ml) was treated with DEAD (456.7 mg, 2.51 mmol), triphenylphosphine (687 mg, 2.51 mmol) and then a solution of diphenylphosphoryl azide (721 mg, 2.51 mmol) in THF (5 ml) at 0°C. After stirring for 1 hour, starting material was absent and the solvent was removed. The product was isolated by column chromatography (flash silica, 15% ethyl acetate in petrol) to give (**166**) (613.2 mg, 85.1%) as an oil; υ_{max} 2980, 2900, 2070, 1570, 1470 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.39 (3H, s), 1.52 (3H, s), 2.11-2.21 (2H, m), 2.76-3.06 (4H, m), 3.16 (1H, dd, *J* = 4, 12.8 Hz), 3.26 (1H, dd, *J* = 7.5, 12.6 Hz), 4.30 (1H, ddd, *J* = 4.2, 7.5, 7.5 Hz), 5.19 (1H, dd, *J* = 6.6, 8.4 Hz), 5.86 (1H, d, *J* = 8.4 Hz); δ_C (68 MHz; $CDCl_3$) 24.26 (CH_2), 25.23 (CH_3), 27.73 (CH_3), 28.96 (CH_2), 29.29 (CH_2), 51.54 (CH_2), 74.24 (CH), 76.74 (CH), 109.14, 124.68 (CH). Compound (**166**) was not characterized by elemental analysis or high resolution mass determination.

(1R,5S,6S)-7-Aza-6-(1,3-dithian-2-yl)-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane (**168**)

A solution of (**166**) (3.07 g, 10.68 mmol) in *n*-octane (30 ml) was heated under reflux for 4 hours under an atmosphere of nitrogen. The solution was allowed to cool to room temperature, then cooled in ice and diluted with dry methanol (30 ml), and sodium borohydride (890 mg, 21.4 mmol) was added. After 30 minutes water was added and the product was extracted with ether (3 portions). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and purified by column chromatography (flash silica, methanol in ethyl acetate) to give (**168**)(6.48 mmol, 60.8%) which crystallized on standing, m.p. 100.9-101.9°C; (Found: C, 50.4; H, 7.44; N, 5.07; $C_{11}H_{19}NO_3S_2$ requires C, 50. 54; H, 7.33; N, 5.36); υ_{max} 2900, 1450, 1360, 1190, 1050; δ_H (270 MHz; $CDCl_3$) 1.34 (3H, s), 1.49 (3H, s), 1.87-2.06 (1H, m), 2.07-2.17 (1H, m), 2.43 (1H, broad), 2.66 (1H, dd, J = 4, 13 Hz), 2.79-2.96 (4H, m), 3.12 (1H, d, J = 13 Hz), 4.27 (1H, d, J = 10.6 Hz), 4.67-4.71 (2H, m). Irradiation of the peak at 1.49 gave NOE enhancements at 1.34, 3.12 and 4.27; *m/z* (C.I.) 262 (mH^+, 35%), 246 (2), 142 (100), 119 (15).

(1R,5S,6S)-7-Aza-6-(1,3-dithian-2-yl)-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane-7-(carboxylic acid-1,1-dimethylethyl ester) (**169**)

A solution of (**168**) (27.4 mg, 0.105 mmol) in dichloromethane (2 ml) was treated with a solution of di-*tert*-butyldicarbonate (23 mg, 0.105 mmol) in dichloromethane (2 ml) and triethylamine (0.1 ml). After 12 hours, the solvent was removed and the product was purified by column chromatography (flash silica, 15% ethyl acetate in petrol) to give (**169**) (33.0 mg, 91%) which crystallized on standing and could be recrystallized from petrol, m.p. 118.5-119.5°C; (Found: C, 53.4; H, 7.66; N, 3.82, $C_{16}H_{27}NO_4S_2$ requires C, 53.15; H, 7.53; N, 3.87%); υ_{max} 2900, 1670, 1450, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.37 (3H, s), 1.48 (9H, s), 1.56 (3H, s), 2.00 (2H,

quintet, J = 5.6 Hz), 2.55-2.77 (2H, m), 2.92-3.15 (2H, m), 3.11 (1H, dd, J = 5.5, 12.2 Hz), 4.09 (1H, dd, J = 8, 12 Hz), 4.20 (1H, broad), 4.45 (1H, broad), 4.75 (1H, dt, J = 7.3, 12.6 Hz), 4.87 (1H, t, J = 6.8 Hz), *m/z* (low eV E.I.) 361 (m^+, 30%), 305 (50), 242 (100), 186 (45), 142 (25).

(1R,5S,6S)-7-Aza-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane-6-carboxaldehyde-7-(carboxylic acid 1,1-dimethylethyl ester) (**170**)

A solution of (**169**) (382.7 mg, 1/06 mmol) in moist ether (10 ml) was treated with thallium (III) trifluoroacetate (630 mg, 1.17 mmol) which, after stirring at room temperature for 12 hours, led cleanly to a new compound . Water was added and the product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the product was purified by short-path column chromatography (flash silica, 40% ethyl acetate in petrol) to give (**170**) (269.1 mg, 93% as an oil which was unstable. (Found: m^+-CHO, 242.1401, $C_{12}H_{20}NO_4$ requires 242.1391, Δ = 3.4 ppm); υ_{max} 3500 (broad), 2950, 1700, 1360 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30 (3H, s), 1.43 (9H, s), 1.49 (3H, s), 3.60 (1H, broad), 3.75 (1H, broad), 4.10 (1H, broad), 4.82 (1H, dt, J = 2.0, 5.8 Hz), 4.99 (1H, t, J = 6.4 Hz), 9.44 (1H, s); *m/z* (C.I.) 272 (mH^+, 1.5%), 256 (10), 242 (30), 216 (95), 200 (25), 186 (55), 172 (60), 142 (100); (70 eV E.I.) 242 (m^+-CHO).

(1R,5S,6S)-7-Aza-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane-6,7-dicarboxylic acid-7-(1,1-dimethylethyl ester) (**171**)

Compund (**170**) (252. mg, 0.093 mmol) was dissolved in a mixture of water (3 ml), carbon tetrachloride (2 ml) and acetonitrile (2 ml). Sodium periodate (80 mg, 0.36 mmol) and ruthenium trichloride (2 mg) were added, and the reaction mixture was stirred rapidly for 6 hours. The product was extracted with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and

concentrated by rotary evaporation. The product was purified by column chromatography (flash silica, 0-20% methanol in ethyl acetate) to give (**171**) (19 mg, 71.2%); (Found: m^+-BOC, 186.0768, $C_8H_{12}NO_4$ requires 186.0765); υ_{max} 3000-3500 cm^{-1}; 2900, 1680, 1370 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.33 (3H, s), 1.43 (9H, s), 1.47 (3H, s), 3.67-3.80 (2H, ABX), 4.51 (1H, d, J = 7.2 Hz), 4.84 (1H, dt, J = 3.7, 5.8 Hz), 4.99 (1H, dd, J = 6.6, 7.3 Hz); *m/z* (C.I.) 288 (mH^+, 1%), 272 (4), 257 (2), 232 (45), 216 (40), 188 (100) (70 eV E.I.) 279 (1%), 272 (1), 256 (1), 216 (25), 186 (m^+-BOC, 10%).

(1R,5S,6S)-7-Aza-3,3-dimethyl-2,4-dioxabicylo[3.3.0]octane-6-carboxylic acid trifluoroacetic acid salt (**172a**)

A solution of (**171**) (15 mg) in TFA (1 ml) was stirred at room temperature for 1 hour. The solvent was removed by rotary evaporation then high vacuum, to give (**172a**). δ_H (270 MHz; D_2O) 1.36 (3H, s), 1.48 (3H, s), 1.39 (dd, J = 4.3, 13.2 Hz), 3.63 (1H, d, J = 13.2 Hz), 4.47 (1H, d, J = 5.2 Hz), 5.11 (1H, dd, J = 4.4, 5.7 Hz), 5.21 (1H, t, J = 5.7 Hz).

(2S, 3S, 4R)-3,4-Dihydroxyproline trifluoroacetic acid salt (**172b**)

Compound (**171**) (16.8 mg, 0.0585 mmol) was dissolved in a mixture of TFA and methanol (10:1, 2 ml) and stirred at room temperature for 5 days. The solvent was removed by rotary evaporation to give (**172b**); δ_H (270 MHz; D_2O) 3.26 (1H, dd, J = 7.9, 8.2 Hz), 3.60 (1H, dd, J = 7.7, 11.7 Hz), 4.52 (2H, m) (1H, obscured by D_2O).

(2R, 3S, 4R)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine hydrochloride salt (**173b**)

A solution of (**170**) (40 mg, 0.148 mmol) in dry methanol (1 ml) was cooled to 0°C and sodium borohydride (20 mg, 0.308 mmol) was added. After 5 minutes, a more polar product had formed. Water (2 ml) was added and the product was extracted

with ether (3 portions). The combined organic extracts were dried with anhydrous sodium sulphate, filtered then concentrated by rotary evaporation, and the product was purified by column chromatography (flash silica, 30-50% ethyl acetate in petrol) to give (**173a**) (15.0 mg, 37%); δ_H (270 MHz; $CDCl_3$) 1.33 (3H, s), 1.47 (9H, s), 1.50 (3H, s), 3.55 (2H, broad), 3.85 (3H, broad), 4.7 (1H, broad), 4.8 (1H, broad).

Compound (**173a**) was dissolved in water (1 ml) and 2N HCl (1 drop), and stirred for 12 hours at room temperature. The solvent was removed by rotary evaporation followed by high vacuum to give (**173b**) which crystallized on standing; (m.p. 156.1-157.1°C, lit;159-161°C[155]; δ_H(270 MHz; D_2O) 3.29 (1H, dd, J = 7.5, 12.1 Hz), 3.63 (1H, dd, *J* = 7.3, 12.1 Hz), 3.83 (1H, m), 3.99 (1H, dd, *J* = 8.3, 12.1 Hz), 4.09 (1H, dd, *J* = 4.9, 12.1 Hz), 4.44 (1H, t, *J* = 4.1 Hz), 6.99 (1H, dt, *J* = 4.0, 7.3 Hz); δ_C (68 MHz; D_2O) 48.14, 58.65, 63.51, 70.84, 70.97; *m/z* (C.I.) 136 (m^++2, 95%), 135 (90), 134 (25), 117 (30), 103 (100).

1-Benzoyl-2-bis(phenylthio)methylene-3-[hydroxy(phenyl) methyl]pyrrolidine (**177**)

A freshly prepared solution of LDA (0.36 mmol) in THF (2 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with a solution of (**117**) (120.4 mg, 0.3 mmol) in THF (1.5 ml), which was added dropwise by syringe. After warming to -60°C over 30 minutes, the orange solution was cooled to -78°C and a solution of benzaldehyde (38 mg, 0.36 mmol) in THF (1 ml) was added dropwise. After warming to room temperature, two more polar products had formed. The reaction was quenched with water (3 ml) and the products were extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and purified by column chromatography (flash silica, 7-35% ethyl acetate in petrol) to give the less polar, unidentified product (46.8 mg) and the more polar product (**177**) (35.0 mg, 23%) as an oil; υ_{max} 3100-3500 (broad), 3050, 2900, 1630, 1570, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.8-2.0 (2H, broad),

3.4 (1H, broad), 3.78 (1H, dt, J = 2.6, 10.2 Hz), 3.91 (1H, dt, J = 1.5, 10.2 Hz), 4.28-4.32 (1H, broad), 4.77 (1H, d, J = 7.8 Hz), 7.00-7.65 (15H, m); *m/z* (70 eV E.I.) 279 (m^+-$(PhS)_2C$, 10%), 247 (3), 157 (10), 149 (55), 120 (40), 105 (100). Compound (**177**)was not characterized by elemental analysis or high resolution mass determination.

General Procedure for Deprotonation/Alkylation of (**71**)

A solution of LDA (1.2 mmol) in THF (3 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with a solution of (**71**) (271 mg, 1.0 mmol) in THF, which was added dropwise by syringe. The reaction mixture was allowed to warm to 0°C over 30 minutes and then stirred for an additional 90 minutes with the temperature kept between -20 and 0°C. The pale yellow solution was then cooled to -78°C and a solution of the electrophile (1-2 equivalents) in THF (3 ml) was added. The reaction mixture was allowed to warm to room temperature then stirred for 2-3 hours. Water (5 ml) was added the product was extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the product was purified by column chromatography (flash silica, ethyl acetate in petrol).

2-[1-(2,2-Dimethylpropanoyl)-3-[hydroxy(phenyl)methyl]pyrrolidin-2-ylidene]-1,3-dithiane (**178**)

The anion derived from (**71**) (267.9 mg, 0.989 mmol) was quenched with benzaldehyde (159 mg, 1.5 mmol) which gave (**178**) (206.1 mg, 55.3%) as a crystalline solid, m.p. 47-50°C; (Found: C, 63.5; H, 7.31; N, 3.71; $C_{20}H_{27}NO_2S_2$ requires C, 63.6; H, 7.21; N, 3.71%); υ_{max} 3300-3500 (broad) 2900, 1630, 1570 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (9H, s), 1.80-2.30 (4H, m), 2.60-2.75 (3H, m), 2.82-2.98 (2H, m), 3.54 (1H, dt, J = 2.5, 7.5 Hz), 3.65-3.80 (2H, m), 4.42 (1H, d, J = 6.9 Hz), 7.25-7.40 (5H,

m); m/z (C.I.) 378 (mH^+, 50%), 377 (30), 360 (45), 292 (10), 271 (100).

2-[1-(2,2-Dimethylpropanoyl)-3-(hydroxymethyl)pyrrolidin-2-ylidene]-1,3-dithiane (**179**)

The anion derived from (**71**) (265.2 mg, 0.978 mmol) was quenched with a suspension of formaldehyde (excess, dried over P_2O_5) in THF which gave (**179**) (241.9 mg, 82.1%) as an oil; υ_{max} 3200-3600, 2900, 1670, 1600 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 1.95-2.20 (4H, m), 2.65-2.95 (4H, m), 3.35-4.70 (5H, m); *m/z* (low eV E.I.) 301 (m^+, 100%), 216 (65), 57 (30), 45 (50). The molecular ion peak did not give satisfactory high resolution mass determination.

2-[3-Benzoyloxymethyl-1-(2,2-dimethylpropanoyl)pyrrolidin-2-ylidene]-1,3-dithiane (**179a**)

A solution of (**179**) (131.1 mg, 0.48 mmol) in dichloromethane (2 ml) was cooled to 0°C under an atmosphere of nitrogen and treated with benzoyl chloride (70 mg, 0.5 mmol), pyridine (80 mg, 1 mmol) and DMAP (5 mg), then allowed to warm to room temperature and stirred overnight. Purification by column chromatography (flash silica, 15-20% ethyl acetate in petrol) gave (**179a**) as an oil (98.3 mg, 50.5%); ν_{max}2950, 1730, 1660, 1600, 1490 cm^{-1}; δ_H(270 MHz, $CDCl_3$) 1.31 (9H, s), 2.08-2.17 (2H, m), 2.65-2.95 (2H, m), 3.64-3.80 (2H, m), 3.85-4.00 (2H, m), 4.26 (1H, dd, J = 7.9, 10.8 Hz), 4.38, (1H, dd, J = 5.7, 10.8 Hz), 7.38-7.47 (2H, m), 7.55 (1H, tt, J = 0.5, 7.4 Hz), 8.03-8.09 (2H, m); *m/z* (C.I.) 406 (mH^+, 100%), 380 (5), 368 (2), 350 (15), 320 (80), 284 (30).

2-[4-[N-(2,2-Dimethylpropanoyl)amino]-2-(hydroxymethyl)buta n-1-oyl]-1,3-dithiane (185)

A solution of (**179**) (132.6 mg, 0.426 mmol) in aqueous acetonitrile (1:4, 10 ml) was treated with mercuric chloride (463 mg, 1.7 mmol) which, after stirring for 9 hours at room temperature, led cleanly to new compound. The product was extracted with dichloromethane/petrol (1:1, 10 ml) and the organic layer was washed with water (1 ml) then brine (1 ml), dried over anhydrous sodium sulphate, filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (flash silica, 60-80% ethyl acetate in petrol) to give (**185**) (76.6 mg, 56.4%) as a white solid which was recrystallized from dichloromethane/petrol to give needles, m.p. 124.8-125.1°C; (Found: C, 52.4; H, 8.01; N, 4.25, $C_{15}H_{23}NO_3S_2$ requires C, 52.63; N, 7.89; N, 4.38%); υ_{max} 3400, 2950, 1710, 1620, 1550, 1470 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.75-1.97 (2H, m), 2.00-2.18 (2H, m), 2.29 (1H, t, J = 5.5 Hz), 2.54-2.64 (2H, m), 3.05-3.20 (3H, m), 3.25-3.45 (2H, m), 3.78-3.85 (2H, m), 4.42 (1H, s), 6.00 (1H, s, broad); *m/z* (70 eV E.I.) 319 (m^+, 2%) 301 (6), 289 (6), 237 (2), 200 (37), 170 (5), 119 (100).

2-[1-(2,2-Dimethylpropanoyl)-3-methylpyrrolidin-2-ylidene]-1.3-dithiane (186)

The anion derived from (**71**) (252.8 mg, 0.93 mmol) was quenched with methyl iodide (170 mg, 1.2 mmol) which gave (**186**) (129.9 mg, 49%) as an oil, which crystallized on standing, m.p. 75-77°C; (Found: C, 58.7; H, 8.30; N, 4.9 $C_{14}H_{23}NOS_2$ requires C, 58.90; H, 8.1; N, 4.91%); υ_{max} 2900, 1630, 1600, 1440 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.07 (3H, d, J = 7.0 Hz), 1.32 (9H, s), 1.92 (1H, quintet, J = 7.3 Hz), 2.02-2.20 (3H, m), 2.63-2.97 (4H, m), 3.28 (1H, dquintet, J = 1.5, 7.2 Hz), 3.70-3.94 (2H, m); *m/z* (low eV E.I.) 285 (m^+, 100%), 271 (25), 200 (300), 165 (7).

2-[1-(2,2-Dimethylpropanoyl)-3-propylpyrrolidin-2-ylidene]-1,3-Dithiane (**187**)

The anion derived from (**71**) (268.9 mg, 0.992 mmol) was quenched with iodopropane (255 mg, 1.5 mmol) which gave (**187**) (224.8 mg, 72.4 mg) as a crystalline solid, m.p. 92.9-93.9°C; (Found: C, 61.3; H, 8.79; N, 4.44; $C_{16}H_{27}NOS_2$ requires C, 61.29; H, 8.68; N, 4.47%); υ_{max} 2950, 1660, 1600, 1470 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.89 (3H, t, *J* = 6.9 Hz), 1.31 (9H, s), 1.20-1.50 (4H, m), 1.73 (1H, dddd, *J* = 2.0, 3.6, 7.6, 12.5 Hz), 1.99 (1H, ddt, *J* = 7.9, 9.5, 12.5 Hz), 2.08-2.18 (2H, m), 2.65 (1H, dt, *J* = 4.2, 13.5 Hz), 2.76 (1H, dt, *J* = 4.9, 13.2 Hz), 2.82-2.97 (2H, m), 3.15-3.24 (1H, m), 3.71 (1H, dt, J = 3.6, 9.5 Hz), 3.87 (1H, dt, J = 7.9, 9.9 Hz); *m/z* (low eV E.I.) 313 (m^+, 100%), 228 (35), 45 (25), 39 (35).

2-[1-(2,2-Dimethylpropanoyl)-3-(prop-2-en-1-yl)pyrrolidin-2-ylidene]-1,3-dithiane (**188**)

The anion derived from (**71**) (270.8 mg, 1.00 mmol) was quenched with allyl bromide (145 mg, 1.2 mmol) which gave (**188**) (204.1 mg, 66%) as a colourless, crystalline solid, m.p. 80-82°C (Found: C, 61.6; H, 8.40; N, 4.44; $C_{16}H_{25}NOS_2$ requires C, 61.69; H, 8.09; N, 4.50%); υ_{max} 2950, 1660, 1600, 1460 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 1.80 (1H, dddd, *J* = 2.4, 4.1, 7.9, 12.3 Hz), 1.95-21.8 (4H, m), 2.24-2.33 (1H, m), 2.66 (1H, dt, *J* = 4.6, 13.4 Hz), 2.77 (1H, dt, *J* = 5.0, 13.2 Hz), 2.83-2.97 (2H, m), 3.27 (1H, ddt, *J* = 2.2, 5.1, 7.9 Hz), 3.70 (1H, dt, *J* = 4.2, 9.8 Hz), 3.86 (1H, dt, *J* = 7.9, 9.8 Hz), 5.00-5.06 (2H, m), 5.73 (1H, ddt, *J* = 7.1, 10.1, 17.0 Hz); *m/z* (low eV E.I.) 311 (m^+, 100%), 226 (25), 57 (55), 39 (50).

2-[1-(2,2-Dimethylpropanoyl)-3-(phenylmethyl)pyrrolidin-2-y lidene]-1,3-dithiane (**189**)

The anion derived from (**71**) (317.7 mg, 1.172 mmol) was quenched with

benzyl bromide (240 mg, 1.40 mmol) which gave (**189**) (364.5 mg, 86.2%) as a colourless liquid; (Found: C, 66.1; H, 7.83; N, 3.66; $C_{20}H_{27}NOS_2$ requires C, 66.44; H, 7.53; N, 3.87%); υ_{max} 3000, 1660, 1600, 1490 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.32 (9H, s), 1.78-1.88 (1H, ddd, *J* = 2.4, 7.5, 13 Hz), 1.87-1.98 (1H, m), 2.02-2.16 (2H, m), 2.42 (1H, dd, *J* = 8.8, 13.6 Hz), 2.69 (2H, tt, *J* = 4.2, 13.8 Hz), 2.82-2.90 (2H, m), 2.90 (1H, dd, *J* = 5.9, 13.4 Hz), 3.45 (1H, ddt, *J* = 2, 6.5, 8.5 Hz), 3.75 (1H, dt, *J* = 3.6, 9.5 Hz), 3.84 (1H, dt, *J* = 8.6, 12 Hz); *m/z* (70 eV E.I.) 361 (m^+, 40%), 314 (2), 286 (5), 276 (100), 255 (2).

2-[1-(2,2-Dimethylpropanoyl)pyrrolidin-3-(carboxylic acid methyl ester)-2-ylidene]-1,3-dithiane (**190**)

The anion derived from (**71**) (465.7 mg, 1.718 mmol) was quenched with methyl chloroformate (195 mg, 2.06 mmol) which gave (**190**) (480.1 mg, 84.89%) as an oil, which crystallized on standing, m.p. 123.4-125.4°C; (Found: C, 54.7; H, 7.16; N, 4.26; $C_{15}H_{23}NO_3S_2$ requires C, 54.68; H, 7.04; N, 4.25%); υ_{max} 2950, 1740, 1630, 1600, 1490 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 2.06-2.30 (4H, m), 2.69-2.96 (4H, m), 3.68 (3H, s), 3.82 (1H, dt, *J* = 3.3, 9.7 Hz), 3.99 (1H, dt, *J* = 8.3, 9.7 Hz), 4.04 (1H, dd, *J* = 2.2, 8.4 Hz); *m/z* (70 eV E.I.) 329 (m^+, 25%) 270 (4), 244 (100), 233 (2), 212 (5), 204 (2), 184 (15).

2-[1-(2,2-Dimethylpropanoyl)pyrrolidin-3-(acetic acid ethyl ester)-2-ylidene]-1,3-dithiane (**191**)

The anion derived from (**71**) (283.7 mg, 1.047 mmol) was quenched with ethyl bromoacetate (350 mg, 2.10 mmol) which gave (**191**) (260.5 mg, 70.2%) as a colourless oil; (Found: m^+, 357.13994; $C_{17}H_{27}NO_3S_2$ requires m, 357.14324, Δ = 9 ppm); υ_{max} 3000, 1740, 1660, 1480 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.26 (3H, t, *J* = 6.9 Hz), 1.31 (9H, s), 1.78-1.86 (1H, m), 2.04-2.23 (4H, m), 2.65-2.93 (5H, m), 3.54-3.65

(1H, m), 3.72 (1H, dt, J = 4.4, 9.9 Hz), 3.89 (1H, dt, J = 7.5, 10 Hz), 4.09-4.16 (2H, m); *m/z* (low eV E.I.) 357 (m^+, 100%), 272 (25), 251 (5), 119 (15), 57 (5).

General Procedure for Hydrolysis of (**71**) and Derivatives

A solution of the ketene thioacetal (1 mmol) in dichloromethane (10 mmol) under an atmosphere of nitrogen was cooled to -30°C. Boron trifluoride etherate (10 mmol)was added by syringe, followed by ethyl acetate (2 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes then stirred for an additional 2-3 hours. The reaction was then quenched with 5% aqueous potassium carbonate (5 ml), the organic layer was separated and the aqueous layer was extracted with 2 further volumes of dichloromethane (2 x 10 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation, and the residue was purified by column chromatography (flash silica, ethyl acetate in petrol) to give the corresponding thioloesters. The thioloesters were not characterized by elemental analysis or high resolution mass determination but, where possible, were converted to the correspondig methyl esters which were characterized by high resolution mass determination.

1-(2,2-Dimethylpropanoyl)-3-(hydroxymethyl)pyrrolidine-2-ca rbothioic acid-S-(3-mercaptopropyl ester) (**192**)

Hydrolysis of (**179**) (90.0 mg, 0.299 mmol) with boron trifluoride etherate gave (**192**) (19.9 mg, 21%); υ_{max} 3300-3600 (broad), 2950, 2550, 1700, 1640, 1490 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (9H, s), 1.40 (1H, t, J = 8.2 Hz), 1.60-2.30 (5H, m), 2.57 (2H, q, J = 7.7 Hz), 2.90-3.05 (2H, m), 3.55-4.05 (4H, m), 4.45-4.58 (1H, m); *m/z* (C.I.) 320 (mH^+, 10), 302 (15), 270 (10), 257 (8), 212 (100), 184 (85). 1H NMR indicates the presence of impurities.

3-(Benzoyloxymethyl)-1-(2,2-dimethylpropanoyl)pyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester (**193**)

Hydrolysis of (**179a**) (270 mg, 0.67 mmol) with boron trifluoride etherate gave (**193**) (196.3 mg, 68.2%) as an oil which NMR revealed to be a single diastereomer; υ_{max} 2950, 2550, 1720, 1670, 1620, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28 (9H, s,), 13.9 (1H, t, J = 8.1 Hz), 1.87 (2H, quintet, J = 7.1 Hz), 2.00-2.15 (1H, m), 1.25-2.35 (1H, m), 2.56 (2H, q, J = 7.1 Hz), 2.60-2.70 (1H, m), 2.94-3.02 (2H, m), 3.70-3.95 (3H, m), 4.37 (1H, d, J = 6.8 Hz), 4.60-4.70 (1H, m), 7.39-8.06 (5H, m); *m/z* (C.I.) (424, mH^+, 5%), 405 (20), 372 (2), 332 (5), 320 (30), 288 (20), 224 (80), 196 (40), 182 (55), 166 (60), 154 (100).

1-(2,2-Dimethylpropanoyl)-3-methylpyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester (**194**)

Hydrolysis of (**186**) (90.3 mg, 0.31 mmol) with boron trifluoride etherate gave (**194**) (70.7 mg, 75.3%) as an oil which NMR revealed to be a mixture of diastereomers (ratio 7:3); υ_{max} 2950, 1700, 1640, 1490, 1410 cm^{-1}; δ_H (270 ,MHz; $CDCl_3$) 1.18 (3H, d, J = 6.6 Hz), 1.28 (9H, s), 1.40 (1H, t, J = 8.2 Hz), 1.87 (2H, quintet, J = 7.2 Hz), 1.80-2.00 (1H, m), 2.08-2.25 (2H, m), 2.57 (2H, q, J = 7.8 Hz), 2.98 (2H, t, J = 7.0 Hz), 3.64-3.95 (2H, m), 4.25 (0.7H, d, J = 6Hz), 4.67-4.73 (0.3H, m); *m/z* (C.I.) 304 (mH^+, 5%), 290 (3), 196 (65), 182 (25), 168 (100), 154 (45).

1-(2,2-Dimethylpropanoyl)-3-propylpyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester (**195**)

Hydrolysis of (**187**) (134.2 mg, 0.428 mmol) with boron trifluoride etherate gave (**195**) (115.6 mg, 81.6%) as a colourless oil which NMR revealed to be a mixture of diastereomers (ratio >20:1); υ_{max} 3000, 2550, 1700, 1640, 1490, 1420 cm^{-1}; δ_H (270

MHz; $CDCl_3$) 0.93 (3H, t, J = 7.0 Hz), 1.29 (9H, s), 1.30-1.40 (2H, m), 1.39 (1H, t, J = 8.1 Hz), 1.55-1.70 (2H, m), 1.87 (2H, quintet, J = 7.2 Hz), 2.03-2.30 (2H, m), 2.57 (2H, dt, J = 7.0, 7.9 Hz), 2.97 (2H, t, J = 7 Hz), 3.87 (1H, dt, J = 7.3, 10.1 Hz), 3.85-3.95 (1H, m), 4.34 (1H, d, J = 5.5 Hz); *m/z* (C.I.) 332 (mH^+, 5%), 313 (4), 246 (2), 224 (55), 196 (100).

1-(2,2-Dimethylpropanoyl)-3-(prop-2-en-1-yl)pyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester (**196**)

Hydrolysis of (**188**) (130.0 mg, 0.418 mmol) with boron trifluoride etherate gave (**196**) (121.7 mg, 88.5%) as a colourless oil which NMR revealed to be a mixture of diastereomers (ratio 10:1); υ_{max} 2950, 2550, 1720, 1640, 1490, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28 (9H, s), 1.40 (1H, t, J = 8.1 Hz), 1.60-1.75 (2H, m), 1.87 (2H, quintet, J = 7.0 Hz), 2.04-2.29 (3H, m), 2.35-2.45 (1H, m), 2.57 (2H, q, J = 7.5 Hz), 2.98 (2H, t, J = 7.1 Hz), 3.65-3.77 (1H, m), 3.82-3.91 (1H, m), 4.42 (0.9H, d, J = 3 Hz), 4.82 (0.1H, d, J = 2 Hz), 5.0-5.15 (2H, m), 5.71-5.85 (1H, m); *m/z* (C.I.) 330 (mH^+, 4%), 311 (25), 296 (2), 279 (2), 222 (60), 194 (100).

1-(2,2-Dimethylpropanoyl)-3-phenylmethylpyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester (**197**)

Hydrolysis of (**189**) (307.0 mg, 0.85 mmol) with boron trifluoride etherate gave (**197**) (284.8 mg, 88.4%) as a colourless oil which NMR revealed to be a mixture of diastereomers (ratio 13:1); υ_{max} 2950, 2550, 1700, 1640, 1490, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28 (9H, s), 1.40 (1H, t, J = 8.1 Hz), 1.55-1.75 (2H, m), 1.88 (2H, quintet, J = 7.0 Hz), 2.03 (1H, sextet, J = 5.6 Hz), 2.55-2.64 (3H, m), 2.96-3.13 (3H, m), 3.69 (1H, dt, J = 7.1, 10.3 Hz), 3.87 (1H, ddd, J = 5.3, 7.1, 10.1 Hz), 4.6 (0.93H, d, J = 5.5 Hz), 4.90 (0.07H, J = 2 Hz); *m/z* (C.I.) 380 (mH^+, 5%), 361 (3), 346 (2), 272 (60), 244 (100).

1-(2,2-Dimethylpropanoyl)pyrrolidine-2-carbothioic acid-S-(3-mercaptopropyl)ester-3-carboxylic acid methyl ester (**198**)

Hydrolysis of (**190**) (152.4 mg, 0.406 mmol) with boron trifluoride etherate gave (**198**) (85.3 mg, 60.8%) as an oil which NMR revealed to be a single diastereomer; υ_{max} 2950, 2550, 1750, 1700, 1630, 1490, 1450, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.28 (9H, s), 1.39 (1H, t, J = 8 Hz), 1.88 (2H, quintet, J = 7 Hz), 2.29 (1H, q, J = 6.5), 2.57 (2H, dt, J = 7.2, 8.1 Hz), 2.97-3.03 (3H, m), 3.75 (3H, s), 3.81-3.92 (2H, m), 5.05 (1H, d, J = 3.5 Hz); *m/z* (C.I.) 348 (mH^+, 10%), 330 (2), 316 (1), 288 (1), 274 (1), 262 (1), 240 (100), 212 (80), 128 (45).

1-(2,2-Dimethylpropanoyl)pyrrolidine-3-acetic acid ethyl ester-2-carbothioic acid-S-(3-mercaptopropyl)ester (**199**)

Hydrolysis of (**191**) (330.5 mg, 0.925 mmol) with boron trifluoride etherate gave (**199**) (168.7 mg, 48.6%) as an oil which NMR revealed to be a single diastereomer; υ_{max} 3000, 2550, 1740, 1680, 1640, 1480, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.27 (3H, t, J = 7.1 Hz), 1.28 (9H, s), 1.40 (1H, t, J = 8 Hz), 1.65-1.77 (2H, m), 1.88 (2H, quintet, J = 7 Hz), 2.28-2.39 (2H, m), 2.57 (2H, q, J = 7 Hz), 2.67-2.74 (1H, m), 2.98 (2H, t, J = 7 Hz), 3.74 (1H, dt, J = 6.8, 10.2 Hz), 3.85-3.96 (1H, m), 4.16 (2H, q, J = 7.1 Hz), 4.38 (1H, d, J = 7 Hz); *m/z* (C.I.) 376 (mH^+, 5%), 357 (20), 268 (65), 240 (100).

General Procedure for Conversion of Thioloesters to Methyl Esters

A solution of the thioloester (1 mmol) in dry methanol (2 ml) was cooled to 0°C under an atmosphere of nitrogen and then treated with a freshly prepared solution of sodium methoxide (5 equivalents) in methanol (2 ml). After stirring at 0°C for 2-3

hours, water (5 ml) was added and the product was extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation and the product was purified by column chromatography (flash silica, ethyl acetate in petrol) to give the corresponding methyl esters.

1-(2,2-Dimethylpropanoyl)-3-methylproline methyl ester (**200**)

Treatment of (**194**) (50.1 mg, 0.165 mmol) with sodium methoxide in methanol gave (**200**) (19.0 mg, 50.7%) as a colourless oil which NMR indicated to be a single diasteromer; (Found: m^+, 227.15203; $C_{12}H_{21}NO_3$ requires m, 227.15214, Δ = 1 ppm); υ_{max} 3000, 1750, 1630, 1490, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.16 (3H, d, *J* = 6.6 Hz), 1.26 (9H, s), 1.55-1.75 (1H, m), 2.06-2.26 (2H, m), 3.62-3.73 (1H, m), 3.73 (3H, s), 3.87 (1H, ddd, *J* = 4.5, 7, 9.5 Hz), 4.02 (1H, d, *J* = 6 Hz); *m/z* (low eV E.I.) 277 (m^+, 30%), 195 (5), 185 (5), 168 (100), 154 (7), 142 (15), 85 (12), 57 (17).

1-(2,2-Dimethylpropanoyl)-3-propylproline methyl ester (**201**)

Treatment of (**195**) (96.3 mg, 0.291 mmol) with sodium methoxide in methanol gave (**201**) (61.6 mg, 69.2%) as a colourless oil which NMR revealed to be a single diastereomer; (Found: m^+, 255.18213; $C_{14}H_{25}NO_3$ requires m, 255.18344, Δ = 5 ppm); υ_{max} 2950, 1760, 1650, 1490, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.92 (3H, t, *J* = 7.5 Hz), 1.26 (9H, s), 1.32-1.44 (2H, m), 1.53-1.69 (3H, m), 2.05-2.22 (2H, m), 3.63-3.74 (1H, m), 3.73 (3H, s), 3.85 (1H, ddd, *J* = 4, 7.5, 10 Hz), 4.13 (1H, d, *J* = 5 Hz); *m/z* (70 eV E.I.) 255 (m^+, 5%), 224 (2), 196 (65), 170 (20), 112 (40), 85 (30), 57 (100).

1-(2,2-Dimethylpropanoyl)-2-(prop-2-en-1-yl)proline methyl ester (**202**)

Treatment of (**196**) (97.7 mg, 0.297 mmol) with sodium methoxide in methanol gave (**202**) (68.7 mg, 91.4%) as a colourless oil which NMR revealed to be a single diastereomer; (Found: m^+, 253.16914, $C_{14}H_{23}NO_3$ requires m, 253.16779, Δ = -5 ppm); υ_{max} 3000, 1760, 1640, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.26 (9H, s), 1.65-1.75 (1H, m), 2.06-2.26 (3H, m), 2.30-2.43 (1H, m), 3.67-3.88 (1H, m), 3.73 (3H, s), 3.79-3.88 (1H, m), 4.19 (1H, d, *J* = 3 Hz), 5.06-5.12 (2H, m), 5.77 (1H, ddt, *J* = 7, 10.5, 17 Hz); COSY shows that the peak at 2.30-2.43 is an allylic proton; irradiation at 2.37 shows NOE enhancements at 4.19 (10.7%), 5.1 (2.7%) and 5.7 (9.3%); *m/z* (low eV E.I) 253 (m^+, 7%), 221 (7), 194 (100), 168 (8), 154 (5), 85 (5), 57 (8).

1-(2,2-Dimethylpropanoyl)-3-(phenylmethyl)proline methyl ester (**203**)

Treatment of (**197**) (251.8 mg, 0.664 mmol) with sodium methoxide in methanol gave (**203**) (179.0 mg, 89.0%) as a colourless oil which NMR revealed wot be a single diastereomer; (Found: m^+, 303.18538, $C_{18}H_{25}NO_3$ requires m, 303.18344, Δ = -6 ppm); υ_{max} 3000, 1760, 1640, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.26 (9H, s), 1.60-1.78 (1H, m), 1.98-2.10 (1H, m), 2.39-2.51 (1H, m), 2.62 (1H, dd, *J* = 9, 13.8 Hz), 2.97 (1H, dd, *J* = 5, 14 Hz), 3.63-3.76 (1H, m), 3.69 (3H, s), 3.84 (1H, ddd, *J* = 5, 7, 10 Hz), 4.25 (1H, d, *J* = 6 Hz), 7.16-7.33 (5H, m); *m/z* (low eV E.I.) 303 (m^+, 15%), 244 (85), 218 (20), 68 (5), 57 (100), 41 (10).

1-(2,2-Dimethylpropanoyl)-3-(phenylmethyl)proline (**204**)

The ester (**203**) (100 mg, 0.33 mmol) was dissolved in 2N sodium hydroxide (2 ml) and heated under reflux for 2 hours, which gave a new compound. Acidification, followed by cooling in ice, caused precipitation of (**204**) (76.3 mg, 80%); δ_H (270 MHz; $CDCl_3$) 1.29 (9H, s), 1.71 (1H, dq, *J* = 6.5, 13 Hz), 2.08 (1H, dq, *J* = 6.4,

13 Hz), 2.58 (1H, dd, J = 8.6, 13.2 Hz), 2.76-2.86 (1H, m), 2.93 (1H, dd, J = 6, 13 Hz), 3.61 (1H, dt, J = 7, 10.2 Hz), 3.88 (1H, dt, J = 7, 10.2 Hz), 4.35 (1H, d, J = 4.8 Hz), 7.18-7.34 (5H, m).

3-(Phenylmethyl)proline (**205**)

A solution of (**204**) (60 mg, 0.208 mmol) in aqueous TFA (1:4) was stirred at room temperature for 2 days. The solvent was removed by rotary evaporation and the product was purified by ion exchange chromatography (DOWEX 50 x 8-10, water then 2N aqueous pyridine) to give (**205**) (31.9 mg, 75%) which could be recyrstallized from ethanol/ether to give colourless needles, m.p. 251-253°C; (Found: C, 69.2; H, 7.35; N, 6.70; $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.37; N, 6.82%); υ_{max} 3300-3600 (broad), 2900, 2300-3100 (broad), 1610, 1460, 1380 cm^{-1}; δ_H (270 MHz; D_2O) 1.80 (1H, dq, J = 7, 14 Hz), 1.96 (1H, dq, J = 7, 14 Hz), 2.65-2.74 (2H, m), 3.09-3.19 (1H, m), 3.30-3.45 (2H, m), 3.80 (1H, d, J = 6.2 Hz), 7.31-7.40 (5H, m); *m/z* (70 eV E.I.) 205 (m^+, 10%), 160 (100), 143 (15), 131 (5), 114 (10), 91 (70). Repeated recrystallization failed to bring the elemental analysis to within the accepted limits

3-Propylproline (**206**)

A solution of (**201**) (61.6 mg, 0.24 mmol) was dissolved in 2N NaOH (2 ml) and heated under reflux for 1 hour. The solution was then acidified, the solvent was removed by rotary evaporation and the residue was dissolved in aqueous TFA (1:4). The solution was heated under reflux for 2 hours, the solvent was removed by rotary evaporation and the residue was purified by ion exchange chromatography (DOWEX 50 x 8-100, water followed by aqueous pyridine) to give (**206**) as an oil (47.0 mg); δ_H (270 MHz; D_2O) 0.89 (3H, t, J = 7.3 Hz), 1.27-1.48 (3H, m), 1.62-1.79 (2H, m), 2.17-2.28 (1H, m), 2.33-2.46 (1H, m), 3.30-3.47 (2H, m), 3.79 (1H, d, J = 7.3 Hz).

Compound (**206**) was dissolved in 2N HCl then the solvent was removed by rotary evaporation followed by high vacuum to give the hydrochloride of (**206**) (41.2 mg, 88.6% from (**201**)) as a colourless crystalline solid, m.p. 138.5-140.5°C (lit.; 131-133°C for cis/trans mixture[176]); δ_H (270 MHz; D_2O) 0.90 (3H, t, J = 7.1 Hz), 1.28-1.49 (3H, m), 1.65-1.80 (2H, m), 2.20-2.32 (1H, m), 2.41-2.53 (1H, m), 3.94 (1H, d, J = 7.7 Hz).

3-Methylproline (**207**)

A solution of (**194**) (50.2 mg, 0.166 mmol) in 2N NaOH (1 ml) was heated under reflux for 1 hour, cooled and acidified with 2N HCl. The solvent was removed by rotary evaporation then the residue was dissolved in aqueous TFA (1:4, 2 ml) and heated under reflux for 2 hours. The solvent was removed and the residue was purified by ion exchange chromatography (DOWEX 50 x 8-100, water then 2N aqueous pyridine) to give (**207**) (20.5 mg, 95.7%) as a 10.2:1 mixture of *trans* and *cis* compounds, m.p. 205-208°C. Recrystallization from ethanol/ether gave a 30:1 mixture, m.p. 218-223°C;(lit. for pure *trans*, 240-248°C[226]); δ_H (270 MHz; D_2O) 1.22 (3H, d, J = 6.8 hZ), 1.67 (1H, dq, J = 8.4, 13 Hz), 2.13-2.25 (1H, m), 2.31-2.47 (1H, m), 3.32-3.47 (2H, m), 3.59 (1H, d, J = 7.8 Hz); peaks due to cis isomer; 0.99 (d, J = 7.3 Hz), 4.06 (d, J = 7.5 Hz).

Pyrrolidine-2,3-dicarboxylic acid (**208**)

A solution of (**198**).(85.3 mg, 0.246 mmol) in 2N NaOH (2 ml) was heated under reflux for 1 hour. The reaction mixture was acidified with 2N HCl, the solvent was removed by rotary evaporation and the residue was dissolved in aqueous TFA. The solution was heated under reflux for 2 hours, the solvent was removed and the residue was purified by ion exchange chromatography (DOWEX 50 x 8-100, water then 2N aqueous pyridine) to give (**208**) (28.4 mg, 72.6%) as a glass which NMR

revealed to be a 26:1 mixture of diastereomers; δ_H (270 MHz; D_2O) 2.17-2.24 (2H, m), 3.30 (1H, dt, J = 5, 8 Hz), 3.37-3.52 (2H, m), 4.45 (1H, d, J = 5.1 Hz); peak due to other diastereomer; 4.30 (d, J = 6 Hz); m/z (C.I.) 160 (mH^+, 100%), 142 (20), 114 (95). We were not able to recrystallize (**208**) either as the free amino acid or as the hydrochloride salt.

Pyrrolidine-3-acetic acid-2-carboxylic acid (**209**)

A solution of (**199**) (119.1 mg, 0.317 mmol) was dissolved in 2N NaOH (1 ml) and heated under reflux for 1 hour. The reaction mixture was cooled then acidified with 2N HCl, and the solvent was removed by rotary evaporation. The residue was dissolved in aqueous TFA (1:4, 2 ml) and heated under reflux for 2 hours. The solvent was removed and the residue weas purified by ion exchange chromatography (DOWEX 50 x 8-100, water then 2N aqueous pyridine) to give (**209**) (40.7 mg, 74.1%) as a glass which NMR revealed to be a 14:1 mixture of diastereomers; δ_H (270 MHz; D_2O) 1.82 (1H, dq, J = 8.2, 13.2 Hz), 2.28-2.40 (1H, m), 2.59 (1H, dd, J = 8.4, 15.6 Hz), 2.67-2.81 (1H, m), 2.87 (1H, dd, J = 4.5, 15.6 Hz), 3.34-3.51 (2H, m), 3.86 (1H, d, J = 8.1 Hz); peak due to diastereomer; 4.48 (d, J = 5.5 Hz). The mass spectrum of (**209**) did not contain a molecular ion.

4-(1,3-Dithian-2-ylidene)-2-methyl-3-oxobutanoic acid ethyl ester (**211**)

A solution of (**1b**) (132 mg, 1 mmol) and (**210**) (192 mg, 1.2 mmol) in *n*-octane (3 ml) was heated under reflux under an atmosphere of nitrogen. After 4 hours, (**1b**) was absent and the product was purified by column chromatography (Kieselgel 60H, 5-12% ethyl acetate in petrol) to give (**211**) (117.5 mg, 45.2%) as a yellow oil. A sample of (**211**) was also prepared as follows; A freshly prepared solution of LDA (20 mmol) in THF (20 ml) was cooled to -78°C and treated with a solution of ethyl acetopropionate (1.44 g, 10 mmol) in THF (8 ml), which was added

dropwise by syringe. After stirring for 15 minutes, a solution of carbon disulphide (760 mg, 10 mmol) in THF (8 ml) was added, resulting in an intense red colour. The reaction mixture was allowed to warm to 0°C over 2 hours, then cooled to -78°C. A further equivalent of LDA (10 mmol) in THF (5 ml) was added and the reaction was stirred for 30 minutes then, treated with a solution of 1,3-dibromopropane (2.02 g, 10 mmol) in THF (5 ml). The reaction mixture was warmed to room temperature over 1 hour, stirred for a further 1 hour and then quenched with saturated aqueous ammonium chloride (10 ml). The product was extracted with ethyl acetate (3 x 15 ml) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered then concentrated by rotary evaporation. The product was isolated by column chromatography (Kieselgel 60H, 5-15% ethyl acetate in petrol) to give (**211**) (293.7 mg, 11.3%); (Found: m^+, 260.0528, $C_{11}H_{16}O_3S_2$ requires m, 260.0539, Δ = -4.9 ppm); υ_{max} 2970, 2950, 1720, 1630, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.20 (3H, t, J = 7.1 Hz), 1.28 (3H, d, J = 7.2 Hz), 2.19 (2H, quintet, J = 7.3 Hz), 2.88 (2H, t, J = 6.5 Hz), 2.94 (2H, t, J = 7.2 Hz), 3.43 (1H, q, J = 7.1 Hz), 4.11 (2H, q, J = 7.1 Hz), 6.58 (1H, s); δ_C (68 MHz; $CDCl_3$) 13.07 (CH_3), 13.91 (CH_2), 27.99 (CH_2), 28.57 (CH_2), 52.32 (CH), 60.88 (CH_2), 112, 118.06 (CH), 165, 170.77,190.17; *m/z* (low eV E.I.) 260 (m^+, 35%), 159 (100).

4-(1,3-Dithian-2-ylidine)-2-methyl-3-oxopentanoic acid ethyl ester (**212**)

A solution of (**1c**) (14.1 mg, 0.107 mmol) and (**210**) (34 mg, 0.215 mmol) in *n*-octane (1 ml) was heated under reflux in an atmosphere of nitrogen for 24 hours, and the product was isolated by column chromatography (Kieselgel 60H, ethyl acetate in petrol) to give (**212**) (14.9 mg, 56%) as a colourless liquid; (Found: m^+, 274.0689; $C_{12}H_{18}O_3S_2$ requires m, 274.0695, Δ = -3.1 ppm, Found: 173.0086, $C_7H_9OS_2$ requires 173.0093, Δ = -5.1 ppm); υ_{max} 2900, 1720, 1630, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.26 (3H, t, J = 7 Hz), 13.9 (3H, d, J = 7.1 Hz), 2.18 (3H, s), 2.00-2.30 (2H, m), 2.84-3.06 (4 H, m), 3.95 (1H, q, J = 7 Hz), 4.18 (2H, q, J = 7 Hz); δ_C (68 MHz; $CDCl_3$)

13.39 (CH_3), 14.01 (CH_3), 17.13 (CH_3), 23.87 (CH_2), 29.26 (CH_2), 29.39 (CH_2), 49.30 (CH), 60.98 (CH_2), 192.70; *m/z* (70 eV E.I.) 274 (m^+, 20), 186 (15), 173 (95), 129 (40), 102 (50), 85 (100).

1,3-Bis-(1,3-dithian-2-ylidene)trimethylene (220)

A freshly prepared solution of BDP (20 mmol) in dichloromethane/toluene (2:1, 60 ml) was treated with a solution of dimethylglutarate (1.60 g, 10 mmol) in dichloromethane (40 ml) and stirred for 3 days at room temperature. The normal work-up procedure was followed by chromatography (flash silica, 4-7% ethyl acetate in petrol) which gave (**220**) (356.4 mg, 12.9%) as a yellow oil; (Found: m^+, 276.0139, $C_{11}H_{16}S_4$ requires m, 276.0133, Δ = 1.5 ppm); υ_{max} 2900, 1570, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.12-2.20 (4H, m), 2.84-2.90 (8H, m), 3.14 (2H, t, *J* = 7.3 Hz), 5.85 (2H, t, *J* = 7.3 Hz); *m/z* (70 eV E.I.) 276 (m^+, 100%), 243 (10), 231 (15), 201 (60), 170 (25), 145 (50).

1.3-Bis-(1,3-dithian-2-ylidene)-2-propyltrimethylene (221)

A solution of (**220**) (200 mg, 0.724 mmol) in dry THF (2 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with a solution of *n*-butyl lithium (0.54 ml, 0.87 mmol). The reaction mixture was allowed to warm to -40°C over 1 hour, then cooled to -78°C and a solution of *n*-butyl bromide (109 mg, 0.796 mmol) in THF (2 ml) was added dropwise by syringe. The solution was allowed to warm to room temperature over 3 hours, then water was added and the product was extracted with ethyl acetae (3 x 5 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and then concentrated and the residue was purified by column chromatography (Kieselgel 60H, 3% ethyl acetate in petrol) to give (**221**) (201.6 mg, 82.9%) as an oil which NMR revealed to be a mixture of the title compound and the corresponding α-adduct (ratio 1.75:1); (Found: m^+-*n*-Butyl, 275.0039,

$C_{11}H_{15}S_4$ requires 275.,0055, Δ = -6.4 ppm); υ_{max} 2900, 1580, 1560, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.88 (3H, t, *J* = 7.1 Hz), 1.22-1.46 (6H, m), 2.00-2.24 (4H, m), 2.60-2.96 (8H, m), 3.84 (1H, tt, *J* = 7.1, 9.5 Hz), 5.70 (2H, d, *J* = 9.5 Hz); peaks due to minor isomer; 0.89 (3H, t, *J* = 7 Hz), 5.64 (1H, dd, *J* = 0.5, 15.0 Hz), 6.50 (1H, d, *J* = 11 Hz), 6.84 (1H, dd, *J* = 11, 15 Hz); *m/z* (C.I.), 332 (m^+, 30%), 275 (75), 201 (100); (70 eV E.I.) 275 (m^+- *n*-butyl, 5%).

2-[3-(1,3-Dithian-2-ylidene)prop-1-enyl]-2-[hydroxy(phenyl)methyl]-1,3-dithiane (223)

A solution of (**220**) (200 mg, 0.724 mmol) in dry THF (2 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with *n*-butyl lithium (0.54 ml, 0.87 mmol). After warming to -40°C and cooling to -78°C, a solution of benzaldehyde (84 mg, 0.796 mmol) in THF (2 ml) was added. The reaction mixture was allowed to warm to room temperature, then water (2 ml) was added and the product was extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the residue was purified by column chromatography (Kieselgel 60H, 5-22% ethyl acetate in petrol) to give (**223**) (99.9 mg, 36%); υ_{max} 3300-3500 (broad), 3020, 2900, 1600, 1580, 1540, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85-2.20 (4H, m), 2.75-2.95 (8H, m), 4.88 (1H, s), 5.56 (1H, d, *J* = 15.2 Hz), 6.45 (1H, d, *J* = 11.0 Hz), 6.88 (1H, dd, *J* = 10.8, 15.2 Hz), 7.29-7.38 (5H, m); *m/z* (70 eV E.I. and C.I.) no peaks above 197. Compound (**223**) was not characterized by elemental analysis or high resolution mass determination.

2-[3-(1,3-Dithian-2-ylidene)prop-2-en-1-yl]-1,3-dithiane (224)

For the preparation of (**224**) see (**223**). Also recovered from the reaction mixture was starting material (24 mg, 12%) and (**224**) (39.4 mg, 19%) as a yellow, crystalline solid, m.p. 71.5-72.5°C); υ_{max} 2900, 1600, 1450, 1400 cm^{-1}; δ_H (270 MHz,

$CDCl_3$) 1.80-2.25 (4H, m), 2.80-2.98 (8H, m), 4.71 (1H, d, J = 8 Hz), 5.67 (1H, dd, J = 7.9, 15.0 Hz), 6.38 (1H, d, J = 10.8 Hz), 6.79 (1H, dd, J = 10.8, 15.0 Hz); *m/z* (C.I.) 277 (mH^+, 100%), 243 (5), 202 (15), 170 (10), 145 (25), 119 (30). Compound (**224**) was not characterized by elemental analysis or high resolution mass determination.

2-[3-(1,3-Dithian-2-ylidene)prop-1-enyl]-2-(2-hydroxyprop-1-yl)-1,3-dithiane (**225**)

A solution of (**220**) (243.8 mg, 0.88 mmol) in THF (2 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with *n*-butyl lithium (0.61 ml, 0.97 mmol), then allowed to warm to -40°C and recooled to -78°C. A solution of propene oxide (excess) in THF (2 ml) was added then the reaction mixture was allowed to warm to room temperature and quenched with water (3 ml). The product was extracted with ethyl acetate (3 x 5 ml) and the combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated and the products were isolated by column chromatography (kieselgel 60H, 3-15% ethyl acetate in petrol) to give (**226**) (8.4 mg, 3.5%) and (**225**) (29.6 mg, 10.1%). Data for (**225**); (Found: m^+, 334.0543, $C_{14}H_{22}OS_4$ requires m, 334.0551, Δ = -3.3 ppm); υ_{max} 3300-3600 (broad), 2900, 1600, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.18 (3H, d, J = 6.2 Hz), 1.91-2.26 (6H, m), 2.78-2.97 (8H, m), 4.17 (ddq, J = 2, 6.5, 9 Hz), 5.69 (1H, dd, J = 0.5, 15 Hz),. 6.48 (1H, d, J = 10.8 Hz), 6.91 (1H, dd, J = 10.8, 15 Hz); *m/z* (70 eV E.I.) 334 (m^+, 1%), 246 (1), 222 (20), 163 (30), 106 (55), 91 (100).

2-[1,3-Bis(1,3-dithian-2-ylidene)propan-2-yl]-2-[3-(1,3-dithian-2-ylidene)prop-1-en-1-yl]-1,3-dithiane (**226**)

For the preparation of (**226**) see (**225**). υ_{max} 2900, 1570, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.00-2.20 (8H, m), 2.65-2.97 (16H, m), 4.41 (1H, t, J = 9.9 Hz), 5.65 (1H, d, J = 15 Hz), 5.80 (2H, d, J = 9.9 Hz), 6.51 (1H, d, J = 10.4 Hz), 6.87 (1H, dd, J = 10.8, 15 Hz); *m/z* (70 eV E.I, C.I.) no m^+ peak. Compound (**226**) was not characterized

by elemental analysis or high resolution mass determination.

2-[1-(prop-2-en-1-yl)pyrrolidin-2-yl]-1,3-dithiane (**229**)

A solution of (**58**) (110.0 mg, 0.582 mmol) in dry THF (3 ml) under an atmosphere of nitrogen was cooled to -78°C and treated with *n*-butyl lithium (0.80 ml, 1.28 mmol). The reaction mixture was allowed to warm to -40°C, then cooled to -78°C and allyl bromide (84.5 mg, 0.79 mmol) was added. After warming to room temperature the reaction mixture was quenched with water (3 ml) and the product was extracted with ethyl acetate (3x5 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation and the product was purified by column chromatography (flash silica, 20% ethyl acetate in petrol) to give (**229**) (57.5 mg, 43.1%) as a colourless oil; (Found: m^+-dithianyl, 110.0959, $C_7H_{12}N$ requires 110.0969, Δ = -10.0 ppm); υ_{max} 3050, 2950, 1630, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.65-2.39 (6H, m), 2.76-2.95 (6H, m), 3.02 (1H, ddt, *J* = 0.5, 7.4, 13.4 Hz), 3.10 (1H, ddd, *J* = 3.6, 6.8, 9.4 Hz), 3.51 (1H, ddt, *J* = 1.5, 5.7, 13.4 Hz), 4.31 (1H, d, *J* = 4.6 Hz), 5.11 (1H, ddt, *J* = 0.5, 1.5, 10.1 Hz), 5.20 (1H, dq, *J* = 1.5, 15 Hz), 5.96 (1H, dddd, *J* = 5.6, 7.3, 10.1, 15.4 Hz); *m/z* (C.I.) 230 (m^+, 15%), 126 (20), 110 (100); (70 eV E.I.) 119 (2%), 110 (100).

2-(Prop-2-en-1-yl)-2-[1-(prop-2-en-1-yl)pyrrolidin-2-yl]-1,3-dithiane (**230**)

A solution of (**58**) (193 mg, 1.02 mmol) in dry THF was cooled to -78°C under an atmosphere of nitrogen, then treated with a solution of *n*-butyl lithium in hexane (1.40 ml, 2.24 mmol). The solution was allowed to warm to 0°C then cooled to -78°C, and allyl bromide (679 mg, 5.6 mmol) was added. Water was added and the product was extracted with ethyl acetate (3 portions). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation and the residue was purified by column chromatography to give (**230**)

(39.0 mg, 14.2%) and the more polar (**229**) (17.6 mg, 7.3%), both as colourless oils. Data for (**230**); υ_{max} 3060, 2920, 1630, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.6-2.05 (6H, m), 2.48-3.06 (8H, m), 3.15-3.28 (2H, m), 3.65-3.75 (1H, m), 5.06-5.20 (4H, m), 5.85-6.15 (2H, m); *m/z* (C.I.) 270 (mH^+, 10%), 206 (1), 150 (6), 126 (4), 110 (100). Compound (**230**) was not characterized by elemental analysis or high resolution mass determination.

4-(1,3-Dithian-2-ylidene)butylcarbamic acid-1,1-dimethylethyl ester (**231**)

A solution of (**58b**) (276.0 mg, 0.955 mmol) in THF (4 ml) under an atmosphere of nitrogen was treated with TMEDA (132 mg, 1.15 mmol), cooled to -78°C and *n*-butyl lithium (0.72 ml, 1.15 mmol) was added. The solution was warmed to -30°C, cooled to -78°C then allyl bromide (115 mg, 0.95 mmol) in THF (2 ml) was added. After warming to 0°C, water was added and the product was extracted with ethyl acetate (3 portions). The combined organic layers were dried over anhydrous sodium sulphate, filtered, concentrated by rotary evaporation then the product was purified by column chromatography (flash silica, 5-15% ethyul acetate in petrol) to give (**231**) (112.2 mg, 40.6%) as a colourless oil; (Found: m^+, 289.1172; $C_{13}H_{23}NO_2S_2$ requires m, 289.1168, Δ = 0.8 ppm); υ_{max} 3330, 2900, 1660, 1500 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.44 (9H, s), 1.60-2.00 (2H, m), 2.11-2.20 (2H, m), 2.25 (2H, q, J = 7.3 Hz), 2.83-2.88 (4H, m), 3.12 (2H, q, broad, J = 6 Hz), 4.6 (1H, broad), 5.92 (1H, t, J = 7.5 Hz); *m/z* (70 eV E.I.) 289 (m^+, 5%), 233 (5), 216 (210), 170 (45), 145 (10), 119 (50), 114 (100).

2-(Pyrrolidine-1-carboxaldehyde-2-yl)-1,3-dithiane (**232**)

A solution of (**58**) (189 mg, 1 mmol) in DMF (2 ml) was treated with imidazole (170 mg, 2.5 mmol) and *tert*-butylchlorodimethylsilane (151mg, 1 mmol) then stirred for 3 days. The product was isolated by column chromatography (flash

silica, ethyl acetate in petrol) to give (232) as a colourless, crystalline solid, m.p. 65.1-67.1°C; (Found: C, 49.8; H, 7.10; N, 6.44; $C_9H_{15}NOS_2$ requires C, 49.73; H, 6.96; N, 6.44%); υ_{max} 2920, 1630, 1390 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.69-2.49 (6H, m), 2.80-2.95 (4H, m), 3.28-3.37 (0.5H, m), 3.42 (0.5H, dt, *J* = 6.6, 9.4 Hz), 3.59-3.73 (1H, m), 4.05 (0.5H, dt, *J* = 3.1, 6.6 Hz), 4.12 (0.5H, d, *J* = 6.9 Hz), 4.28-4.35 (0.5H, m), 4.92 (0.5H, d, *J* = 4.4 Hz), 8.29 (0.5H, s), 8.37 (0.5H, s); *m/z* (70 eV E.I.) 217 (m^+, 20%), 186 (2), 145 (10), 119 (100), 98 (65).

2-[1-(*tert*-Butyldimethylsilyl)pyrrolidin-2-yl]-1,3-dithiane (233)

A solution of (58) (899 mg, 4.75 mmol), DBU (0.85 ml, 5.7 mmol) and *tert*-butylchlorodimethylsilane (790 mg, 5.23 mmol) in toluene (10 ml) was heated under reflux for 2 hours, which gave a precipitate of DBU-HCl. The reaction mixture was cooled, filtered, the solvent was removed and then the product was purified by column chromatography (flash silica, ethyl acetate in petrol) to give (233) (100%) as a colourless oil; (Found: m^+-dithianyl, 184.1530; $C_{10}H_{22}NSi$ requires 184.1521, Δ = 4.5 ppm); υ_{max} 2950, 1460, 1250 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0.09 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 1.58-2.17 (6H, m), 2.70-2.92 (4H, m), 3.00 (1H, ddd, *J* = 6.6, 7.9, 9.9 Hz), 3.12 (1H, ddd, *J* = 3.7, 7.7, 10 Hz), 3.63-3.69 (1H, ddd, *J* = 4, 5, 7 Hz), 4.15 (1H, d, *J* = 5.1 Hz); *m/z* (C.I.) 304 (mH^+, 20%), 288 (2), 246 (10), 184 (100); (70 eV E.I.) 246 (5%), 184 (100).

5-Aza-1-azido-4,9-bis(1,3-dithian-2-ylidene)nonane-5-carbox ylic acid phenylmethyl ester (234)

A solution of (34) (212.2 mg, 0.986 mmol) in dichloromethane (3 ml) was treated with boron trifluoride etherate (140 mg, 1.0 mmol) at room temperature. After 90 minutes, the solution was cooled to 0°C and treated with pyridine (80 mg, 1 mmol) and benzyl chloroformate (172 mg, 1.0 mmol) then stirred for 1 hour. The solvent was

then removed and the product was isolated by column chromatography (flash silica, 10-30% ethyl aceate in petrol) to give (**234**) (56.7 mg, 25%) as an oil; υ_{max} 2940, 2100, 1700, 1630 cm^{-1}; δ_H 270 MHz; $CDCl_3$) 1.80-2.35 (10H, m), 2.55-2.65 (2H, m), 2.70-2.82 (4H, m), 2.90-2.98 (4H, m), 3.27-3.35 (2H, m), 3.61-3.66 (2H, m), 5.19 (2H, s), 5.51 (1H, t, J = 4 Hz), 7.30-7.43 (5H, m); *m/z* (C.I.) 403 (mH^+-BnOCO 5%), 391 (1), 369 (1), 321 (10). Compound (**234**) was not characterized by elemental analysis or high resolution mass determination.

2-[(1R,2R,3R)-1,2,3,4-Tetrahydroxybutan-1-yl]-1,3-dithiane (**235a**)

A solution of D-ribose (24.5 g ,163 mmol) in concentrated HCl (25 ml) was cooled in ice and treated with propane-1,3-dithiol (17 ml, 171 mmol). After stirring for 1 hour, saturted aqueous sodium chloride (100 ml) was added at 0°C and the reaction mixture was allowed to stand for 3 hours[208]. Excess propane-1,3-dithiol was removed by extraction with dichloromethane (2 x 50 ml) then the product was extracted with ethyl acetate (8 x 200 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered then concentrated by rotary evaporation to give (**235a**) as a white solid, (14.5 g, 37%), which could be recrystallized from ethyl acetate/petrol, m.p. 97-98°C; (Found: C, 39.6; H, 6.5; $C_8H_{16}O_4S_2$ requires C, 39.98; H, 6.71%); υ_{max} 3200-3500 (broad), 2900, 1450 cm^{-1}; δ_H (200 MHz; D_6-DMSO) 1.63-1.85 (1H, m), 1.92-2.08 (1H, m), 2.71 (1H, ddd, J = 3, 10, 14 Hz), 2.80-2.98 (3H, m), 3.40 (1H, dd, J = 5.5, 11 Hz), 3.51-3.71 (4H, m), 4.38 (1H, d, J = 3 Hz), 4.5-4.7 (4H, broad); *m/z* (C.I.) 258 ($m+NH_4^+$, 100%), 240 (m^+, 20), 223 (20), 205 (12), 187 (15), 119 (15). We subsequently learnt of a similar report describing the preparation of (**235a**)[220].

(4R,5R)-5-(1,3-Dithian-2-yl)-4-[(4R)-2,2-dimethyl-1,3-dioxalan-4-yl]-2,2-dimethyl-1,3-dioxalane (**235**)

A solution of (**235a**) (1.3 g, 5.4 mmol) in acetone (90 ml) was treated with

anhydrous copper sulphate (3.2 g, 20 mmol) and concentrated sulphuric acid (0.6 ml)[209]. After stirring overnight, sodium carbonate was added, the reaction mixture was filtered and the solvent was removed by rotary evaporation to give an oil. Chloroform (50 ml) was added and the solution was washed with saturated sodium hydrogencarbonate (5 ml) then water (5 ml). The organic layer was dried over anhydrous sodium sulphate, filtered then concentrated and the products were separated by column chromatography (kieselgel 60H, 20% ethyl acetate in petrol) to give the less polar, undesired isomer (386.3 mg, 22.3%) and the more polar (**235**) (959.1 mg, 55.5%) as an oil; (Found; C, 50.2; H, 7.0; $C_{14}H_{24}O_4S_2$ requires C, 52.47; H, 7.55%); υ_{max} 3000, 2950, 1380 cm^{-1}; δ_H (200 MHz; DMSO-D_6) 1.30 (3H, s), 1.32 (6H, s), 1.40 (3H, s), 1.70-1.90 (1H, m), 1.95-2.10 (1H, m), 2.80-3.00 (4H, m), 3.72-3.97 (2H, m), 4.02-4.16 (2H, m), 4.30-4.55 (2H, m); *m/z* (C.I.) 338 (m+NH^+_4, 10%), 321 (mH^+, 30), 263 (100), 205 (60), 119 (45).

The minor isomer could be recrystallised from ether/petrol to give a colourless crystalline solid, m.p. 76-77°C; (Found: C, 52.6; H, 7.75; $C_{14}H_{24}O_4S_2$ requires C, 52.47; H, 7.55%); υ_{max} 2950, 1460, 1370 cm^{-1}; δ_H (270 ,Hz; $CDCl_3$) 1.36 (6H, s), 1.43 (3H, s), 1.54 (3H, s), 1.80-2.14 (2H, m), 2.80-2.97 (4H, m), 3.91 (1H, dd, *J* = 5.3, 8.6 Hz), 4.08-4.16 (2H, m), 4.42-4.47 (2H, m), 4.61 (1H, dt, *J* = 6, 9.3 Hz); *m/z* (low eV E.I.) 320 (m^+, 25%), 161 (60), 143 (100), 119 (40).

(4R,5R)-4-[(1R)-1,2-Dihydroxyethan-1-yl]-5-(1,3-dithian-2-yl)-2,2-dimethyl-1,3-dioxolane (**236**)

A solution of (**235**) (925 mg, 2.72 mmol) in a mixture of methanol (25 ml) and 2N HCl (2 ml) was stirred at room temperature for 4 hours and then neutralized with sodium carbonate[210]. The solution was filtered then concentrated by rotary evaporation, and the product was extracted with ethyl acetate (3 portions). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and

concentrated by rotary evaporation and the product was purified by column chromatography (flash silica, 40% ethyl aceate in hexane) to give (**236**) (251.7 mg, 31.1%) as an oil; (Found: m^+, 280.0774; $C_{11}H_{20}O_4S_2$ requires m, 280.0801, Δ = -10.5 ppm).

; υ_{max} 3200-3500 (broad), 2900, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.38 (3H, s), 1.43 (3H, s), 1.85-2.02 (1H, m), 2.06-2.18 (1H, m), 2.65-2.85 (2H, broad), 2.85-3.03 (4H, m), 3.80-3.94 (2H, m), 4.02-4.08 (1H, m), 4.33-4.40 (2H, m), 4.54 (1H, m); *m/z* (70 eV E.I.) 280 (m^+, 2%), 265 (5), 161 (20), 119 (100)

(1S,8S,9R,13R)-11,11-Dimethyl-10,12,14-trioxa-2,6-dithiatri cyclo[6.5.1.$0^{9,13}$]tetradecane (**237**)

For the synthesis of (**237**) see (**238**). Data for (**237**); (Found: m^+, 262. 0693; $C_{11}H_{18}O_3S_2$ requires m, 262.0697, Δ = -1.9 ppm); υ_{max} 2900, 1440, 1400, 1300 cm^{-1}, δ_H (270 MHz; $CDCl_3$) 1.35 (3H, s), 1.52 (3H, s), 1.85-2.00 (1H, m), 2.04-2.17 (1H, m), 2.76-2.99 (4H, m), 3.98-4.07 (2H, m), 4.09 (1H, d, *J* = 7.3 Hz), 4.20 (1H, dd, *J* = 1.7, 7.3 Hz), 4.81-4.89 (2H, m); *m/z* (70 eV E.I.) 262 (m^+, 5%), 249 (2), 204 (5), 187 (2), 159 (2), 119 (100).

(4R,5R)-4-[(1R)-1-Hydroxy-2-(4-methylphenylsulphonyloxy)ethan-1-yl]-5-(1,3-dithian -2-yl)-2,2-dimethyl-1,3-dioxolane (**238**)

A solution of (**236**) (195.9 mg, 0.699 mmol) in dichloromethane (5 ml) was treated with pyridine (110 mg, 1.4 mmol), cooled in ice then tosyl chloride (134 mg, 0.70 mmol) was added. After stirring at room temperature for 3 days, two new products had formed. Saturated sodium chloride (6 ml) was then added and the products were extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered, then concentrated by rotary evaporation and the products were separated by column chromatography (flash silica, 10-40% ethyl

acetate in petrol) to give the less polar (**238**) (35.8 mg, 12%) and the more polar (**237**) (105 mg, 57.3%). Data for (**238**); 3500, 2900, 1590, 1350 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.32 (3H, s), 1.36 (3H, s), 1.82-1.98 (1H, m), 2.03-2.09 (1H, m), 2.45 (3H, s), 2.82 (1H, broad), 2.82-2.98 (4H, m), 3.79 (1H, dd, J = 2, 9.2 Hz), 4.06-4.14 (1H, m), 4.24-4.30 (2H, m), 4.35-4.39 (1H, m), 4.46 (1H, d, J = 2 Hz), 7.35 (2H, d, J = 7.8 Hz, part of AA'BB'), 7.83 (2H, d, J = 8.4 Hz, part of AA'BB'; *m/z* (70 eV E.I.) 262 (m^+-TsOH, 5%), 119 (100), 105 (30). Compound (**238**) was not characterized by elemental analysis or high resolution mass determination.

(4S,5R)-4-(1,3-Dithian-2-ylidenemethyl)-2,2-dimethyl-5-(4-methylphenylsulphonyloxy methyl)-1,3-dioxolane (**239a**)

A solution of (**165**) (698.0 mg, 2.66 mmol) in dichloromethane (10 ml) was cooled to 0°C and treated with pyridine (2 ml, 25 mmol) and tosyl chloride (508 mg, 2.66 mmol). After 20 hours at room temperature, two products had formed. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (flash silica, ethyl acetate in petrol) to give (**239a**) (755.9 mg, 68.3%) which crystallized on standing and (**239b**) (122.4 mg, 17.6%) as an oil. Data for (**239a**); m.p. 53.9-54.9°C; (Found: C, 47.7; H, 5.22; $C_{18}H_{24}O_5S_3$ requires C, 51.89; H, 5.81%); υ_{max} 2970, 2900, 1570, 1350 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.33 (3H, s), 1.36 (3H, s), 2.12-2.21 (2H, m), 2.45 (3H, s), 2.78-3.05 (4H, m), 3.87 (1H, dd, J = 6.6, 10.2 Hz), 3.98 (1H, dd, J = 4.6, 10.2 Hz), 4.32 (1H, dt, J = 4.6, 6.6 Hz), 5.16 (1H, dd, J = 6.4, 8.4 Hz), 5.71 (1H, d, J = 8.4 Hz), 7.27 (2H, d, J = 7.9 Hz, part of AA'BB'), 7.82 (2H, d, J = 8.2 Hz, part of AA'BB'); δ_C (68 MHz; $CDCl_3$) 21.60 (CH_3), 24.26 (CH_2), 25.27 (CH_3), 27.54 (CH_3), 28.93 (CH_2), 29.22 (CH_2), 68.60 (CH_2), 74.02 (CH), 75.02 (CH), 109.27, 123.48 (CH), 128.05 (CH), 129.81 (CH), 132.89, 144.79; *m/z* no molecular ion in 70 eV E.I. or C.I.

(1S,6S)-3-[(3-Azidopropyl)thio]-8,8-dimethyl-7,9-dioxa-4-thiabicyclo[4.3.0]non-2-ene (**240**)

A solution of (**239a**) (591.5 mg, 1.42 mmol) in DMF (4 ml) was treated with sodium azide (500 mg, 8.0 mmol), and heated under reflux in an oil bath at 120°C for 20 minutes. The reaction mixture was cooled and the products were isolated by column chromatography (flash silica, ethyl acetate in petrol) to give a mixture of (**166**) and (**240**) (ratio 1:1, 328.6 mg, 81%) as an oil. Thermolysis of the mixture (76 mg, 0.265 mmol) in octane for 4 hours resulted in cyclisation of (**166**), and (**240**) could be recoverred unchanged (35.2 mg, 46%); υ_{max} 2900, 2080, 1570, 1360 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.38 (3H, s), 1.47 (3H, s), 1.82-1.95 (2H, m), 2.60-2.86 (3H, m), 3.05 (1H, ddd, J = 6.2, 7.1, 13.4 Hz), 3.42 (2H, t, J = 6.6 Hz), 4.26 (1H, ddd, J = 4.6, 5.9, 10.6 Hz), 4.48 (1H, dd, J = 4.4, 5.9 Hz), 6.20 (1H, d, J = 5.0 Hz); *m/z* (C.I.) 288 (mH^+, 20%), 242 (70), 230 (30), 202 (25), 154 (100). Compound (**240**) was not characterized by elemental analysis or high resolution mass determination.

2-[3-Chloromethyl-1-(2,2-dimethylpropanoyl)pyrrolidin-2-ylidene]-1,3-dithiane (**242**)

A solution of (**179**) (42.6 mg, 0.137 mmol) in dichloromethane (1 ml) was treated with tosyl chloride (26 mg, 0.137 mmol), pyridine (21 mg, 0.27 mmol) and DMAP (1 mg) at 0°C under an atmosphere of nitrogen. After stirring at room temperature for 18 hours, a small amount of two new, less polar products had formed. The reaction mixture was then heated under reflux using an oil bath at 65°C for 4.5 hours. After this time starting material and the more polar product were absent from the reaction mixture. The solvent was removed and the product was isolated by column chromatography (flash silica, 10-15% ethyl acetate in petrol) to give (**242**) (20.3 mg, 48.8%) as an oil; υ_{max} 2950, 2250, 1660, 1600, 1490, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 2.07-2.21 (4H, m), 2.69 (1H, dt, J = 4.7, 13.6 Hz), 2.79-2.99 (3H, m), 3.22 (1H, t, J = 10.6 Hz), 3.52 (1H, ddt, J = 3.8, 7.5, 12 Hz), 3.73 (1H, ddd, J = 5, 8, 10.5

Hz), 2.82 (1H, dd, J = 4.2, 10.8 Hz), 3.94 (1H, dt, J = 7.9, 9.9 Hz); *m/z* (C.I.) 320 (mH^+, 5%), 302 (10), 290 (10), 284 (2), 230/232 (95), 202/204 (100), 118 (50), 85 (75).

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PUBLICATIONS

Publications

Work described in this thesis has been published in the following papers;

1. "Ketene-S,S-acetals as 1,3-dipolarophiles. Reactivity towards electron deficient azides.", W.O. Moss, R.H. Bradbury, N.J. Hales and T.C. Gallagher, *Tetrahedron Lett.*, 1988, **29**, 6475-6478.

2. "Ketene-S,S-acetals as 1,3-dipolarophiles. Applications to the synthesis of cyclic amino acids.", W.O. Moss, R.H. Bradbury, N.J. Hales and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1990, 51-53.

3. "Generation of α-amino acid homoenolate equivalents. Synthesis of 3-substituted prolines." W.O. Moss, R.H. Bradbury, N.J. Hales and T. Gallagher, *Tetrahedron Lett.*, 1990, in press.